VOLUME 5 MAY 1956 NUMBER 2

AUSTRALASIAN ANNALS OF MEDICINE

Journal of The Royal Australasian College of Physicians

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The journal is published quarterly in February, May, August, and November. The subscription rate is three pounds per annum, payable in advance to The Royal Australasian College of Physicians, 145 Macquarie Street, Sydney. Advertising rates may be obtained on application to Australasian Medical Publishing Company Limited, Seamer and Arundel Streets, Glebe, Sydney.

AUSTRALASIAN ANNALS OF MEDICINE

VOLUME 5 MAY, 1956 NUMBER 2

THE MACROSCOPIC ANATOMY OF PULMONARY EMPHYSEMA[1]

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" Confusion now hath made his masterpiece "
MACBETH, II, 3, 71

To the pathologist, the term pulmonary emphysema indicates a chronic destructive lung disease characterized by enlargement of existing air spaces in the lung parenchyma.

As the word emphysema derives from the Greek for " inflated ", it has been prefixed by " acute obstructive ", " interstitial " and " surgical " to describe other conditions which are distinct from what is ordinarily referred to simply as emphysema. This terminological point serves well as a forewarning of how much confusion exists in the study of this enigmatic condition.

The ætiology of pulmonary emphysema is unknown ; no single hypothesis explains more than a small number of the recorded observations and most postulates are completely unsatisfactory (Christie, 1954). In particular, the morphology is in a confused state, so that, lacking a sound knowledge of the structural evolution of the disease, investigators in other fields should be aware that many of their conclusions are of limited significance.

Two problems are immediately encountered when emphysematous lungs are examined macroscopically. The first is a question of semantics. Observations have been selected and organized to fit *a priori* hypotheses of origin, even though the observer usually concludes that the ætiology remains obscure. An attempt is made in this paper to arrange observations in a classification containing no ætiological assumptions. Purely descriptive names are used, so that such terms as " compensatory " or " senile " emphysema will not be found.

[1] Received for publication on January 3, 1956.

The second problem is that of the evolution of the disease. Pulmonary emphysema evolves morphologically to an extreme degree before physiological, biochemical and finally clinical diagnostic criteria are evoked. Morphology therefore provides virtually the sole information of the early stages of the disease. The only method of approach to this problem is through the accumulation of a large mass of unselected material, and its subsequent correlation.

HISTORICAL ANALYSIS

In 1819 Laennec published his great work " *De l'auscultation médiate, ou traité du diagnostic des maladies des poumons et du cœur, fondé principalement sur ce nouveau moyen d'exploration* ". This study contains the first definite and clear description in medical literature of emphysema, which he observed to be associated with chronic bronchial disease. He considered that the ætiology of the disease must in some way be due to these bronchial lesions (Laennec, 1834).

Little was added to this classical contribution until the middle of the century, when technical advances permitted the use of " the microscope as a means to gain new insight into pathological processes " (Virchow, 1855). Following Virchow's warning that " this is not the time of systems, this is the time of research of details " (Virchow, 1847), there was such a mass of histological observations that for the next forty to fifty years interest and hypotheses centred on the anatomical minutiæ of the alveolar wall and its elastic fibres (Greenhow, 1867, 1868 ; Auld, 1893 ; Grawitz, 1893 ; Sudsuki, 1899). The breadth of vision of

Laennec seemed to be lost, except in the occasional seer.

One such was A. T. H. Waters, who, in 1862, published in London a book entitled "Emphysema of the Lungs". The early chapters deal with the anatomy of the disease. The observations and their classification would withstand criticism today—much better, indeed, than many more recent works. It is only when the final chapters are read that one abruptly realizes the primitive knowledge of the clinical aspects of the disease and of lung function; then it becomes clear why the problem was not penetrated further.

The simple truth was that the mass of observations collected by anatomists, though essential as a basic framework, contributed virtually nothing at that stage to the elucidation of the ætiology of this condition. Moreover, by the end of the century the advances of pathological anatomy had so outstripped the attendant, but still embryonic, sciences of experimental pathology and pathological physiology, that its study became, inevitably, an end in itself, frequently esoteric and removed from reality. A revolution by the thinkers of the period was inevitable.

This century has thus seen a great shift of accent in the study of disease. The knowledge and techniques of experimental pathology, physiology, biochemistry and clinical investigation have expanded prodigiously. So much so that anatomy, the giant of the last century, has been overshadowed.

The experimental production of emphysema, begun with great hopes, has however yielded a disappointingly poor harvest (Harris and Chillingworth, 1919; Paine, 1940; Rasmussen and Adams, 1942). This is due, first to the great, and indeed, usually insurmountable problems attending the experimental study of any chronic disease and, secondly, to the circumstance that the ætiology is so obscure that a definite approach has never been indicated.

On the other hand the investigation of clinical emphysema by numerous physiological techniques has increased greatly and the names of Baldwin and Cournand, Christie, Donald, Comroe and many others are familiar for their work in this field. The ætiology of emphysema, however, is just as obscure now as it was one hundred and thirty years ago. Present studies of lung function, dealing as they do with the whole pulmonary system or at best a lung or perhaps a lobe, permit an accurate study only of average function of an anatomical lung unit. Too often this "average unit" is given a reality which is non-existent. Similarly, the reduction of lung function in pulmonary emphysema has been expressed as the sum of the activity of a hypothetical part which has no function added to a residual part with normal function. These departures from reality suggest that the fate of the nineteenth century anatomist is overtaking the twentieth century lung physiologists.

Concomitant with this expansion of knowledge, a curious dichotomy of the studies of structure and function has developed. The opinion that morphology has nothing more to offer is still prevalent and the value of this method of investigation is often doubted.

If this attitude is not to control investigation a change of point of view of both the morphologist and his critics is necessary. Study of structure should not be the limited, static and two-dimensional approach of the ninteeenth century, and should show an alert readiness to take advantage of advances in other fields. Little evidence of this change in outlook is apparent in the study of emphysema earlier in this century (see the reviews of Loeschcke, 1928; and Kountz and Alexander, 1934), but today there is an increasing interest in the study of anatomy in its proper perspective, not as an end in itself, but as an integral part of the investigation of a disease process.

This and subsequent papers are intended to present the morphology of emphysema in a framework of space and time. They intend to indicate that this can provide a basis for clearer understanding of this puzzling condition.

Material and Methods

An attempt was made to study lungs showing all types and stages of emphysema. Material from 180 patients was examined, part (131 cases) being obtained from personally conducted autopsies. The remainder (49 cases) was provided by colleagues.

Of the 131 cases personally handled, 50 did not show obvious emphysema, but when they were examined closely, minor degree of localized emphysematous change could always be found. These lungs would ordinarily be described as "normal" and are referred to as such in the text.

All lungs were fixed in a distended state with 10% formalin acetate. In the large majority this was effected by running the solution into the trachea or main bronchus, taking care not to overdistend the lungs. Nine specimens were fixed in the cadaver within two hours of death by intravenous

fixative at a pressure of 60 centimetres of water via the femoral vein, the femoral artery being simultaneously opened. Distortion by gravitational flattening is avoided by this technique, and the excellent results that it gives (Loeschcke, 1928) have been satisfyingly confirmed.

Study of the lungs, once the tissue had hardened, was generally accomplished by cutting slices of 1·0 to 1·5 centimetres' thickness. Vacuum fixation was used to remove air prior to photography, the specimen being photographed under water.

Twenty-eight such slices exhibiting emphysema were cut into large sections by the technique of Gough and Wentworth (1951), their modification of freezing the block to harden it being consistently used; it was found thoroughly satisfactory. To improve the result with grossly emphysematous lungs, some lungs were washed out for forty-eight hours before being cut, warmed to 40° C. in a water bath, filled with the gelatin solution by way of the cannulated bronchus and, after setting, were then cut into 1·5 centimetre slices. A slice was fixed to the block and frozen. This technique is essential to preserve in the sections the appearance of large thin-walled bullæ or gross emphysema. It was not persisted with throughout because it precludes subsequent histological examination.

INCIDENCE

As the material was highly selected, it is impossible to gain from it indication of the general incidence of emphysema. For this reason an analysis was made of 2,000 consecutive autopsies, performed by several pathologists at the Royal Melbourne Hospital over the period from March, 1953, to December, 1955. The figures presented here are therefore quite independent and separate from the cases specially studied at autopsy.

These 2,000 autopsies revealed that:

1. The syndrome of chronic bronchitis and pulmonary emphysema was regarded as the primary cause of death in 52 cases (2·6%). Of these, lung infection dominated the final illness in 24 cases, congestive cardiac failure in another 24 cases, and in four cases a spontaneous pneumothorax was the immediate cause of death. British figures, as might be expected on climatic considerations, are considerably higher than this (Stuart Harris, 1954; Oswald, 1953).

2. Pulmonary emphysema (of any type) was felt to be sufficiently advanced to contribute to the patient's ill health, but was not regarded as directly related to the final illness in another 82 cases (4·1%).

3. Of the total of 134 patients (6·7%), only 12 were female. If cases in which the emphysema was associated with prolonged bronchial asthma (12 cases), definite pneumonoconiosis (14 cases) or extensive tuberculosis (six cases), are removed, a group of 97 males and five females remains. The male to female ratio for all cases is therefore 10 to 1, and in the cases generally classified as chronic bronchitis and emphysema the ratio is nearly 20 to 1. In Britain, Stuart-Harris (1954) found the ratio to be 9 to 1, and Oswald (1953) between 4 and 5 to 1.

The material personally examined and discussed in this paper suggests that subclinical generalized change at death is at least three times as common as clinical emphysema, so that some degree of the generalized condition will be found in at least 25% of autopsies.

CLASSIFICATION

There are few of the following observations on the macroscopic anatomy of emphysema that cannot be found somewhere in the literature. Loeschcke (1928) described many of them. It is astonishing, therefore, that the whole subject has not been previously presented in the framework of a purely descriptive classification. Such a classification based on the cases investigated is offered here.

(1) Localized emphysema (61 cases). Most of the lung is macroscopically normal but at one or several sites there is localized formation of emphysema. This group is subdivided into:

- (*a*) Lesions clearly restricted to anatomical units.
- (*b*) Lesions not apparently related to anatomical units.

(2) Generalized emphysema (119 cases). Most of the lung is macroscopically involved and no segment is unaffected.

- (*a*) Without localized accentuation (89 cases). All parts of the lung are relatively uniformly affected by the process. Two forms are described:
  - (i) Focal or centrilobular generalized emphysema. The process affects the centre of the secondary lobules.
  - (ii) Diffuse generalized emphysema. No lobular pattern is seen, all the parenchyma being affected.
- (*b*) With local accentuation (30 cases). Two main forms are described:
  - (i) Multiple local lesions. This form is merely an extreme form of 1 (*a*).
  - (ii) Generalized emphysema with superimposed localized emphysema.

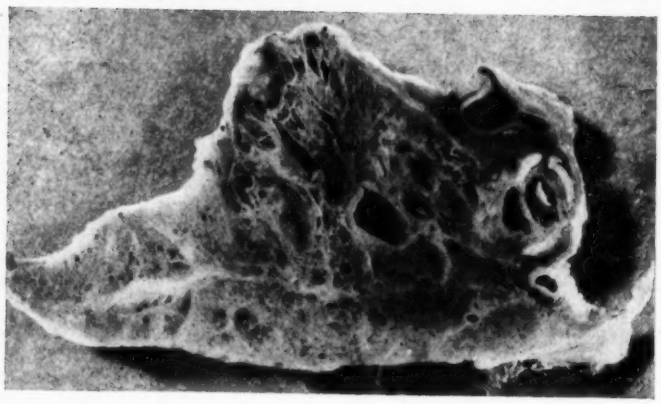

FIGURE I

Localized emphysema. The apical segment of the lower lobe has been cut horizontally, with the lower lobe bronchus and artery on the right. One subsegment is largely emphysematous and the bronchus is bronchiectatic. No other emphysema or bronchiectasis was found in the lungs. (×2)

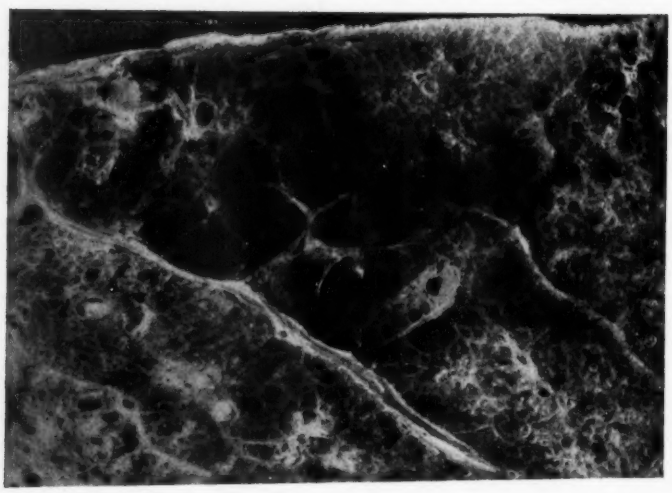

FIGURE II

Localized emphysema. Emphysema related to two ectatic bronchioles. The process is limited sharply by the relatively thick septum running obliquely down from the upper left, but is less well demarcated at the thinner interlobular septa. (×3)

(1) LOCALIZED EMPHYSEMA (61 Cases)

Small areas of emphysema are extremely common in otherwise macroscopically normal lungs. The 50 apparently "normal" lungs all showed, on careful examination, at least a tiny area of emphysema somewhere in the lungs; the youngest subject was aged sixteen years.

The localized lesions fall readily into the two groups described, relatively few examples being difficult to place.

(*a*) *Lesions Clearly Related to Anatomical Units*

Large lesions clearly related to anatomical units are rarely overlooked, but are uncommon. Once acute obstructive emphysema is excluded, emphysema restricted, for instance, to one lobe, is regularly associated with obvious bronchiectasis of the lobar bronchus and its branches; bronchiectatic lobes, on the other hand, are only occasionally emphysematous. No example of emphysema affecting the whole of a bronchiectatic lobe was found, but some part of a bronchiectatic lobe was emphysematous in five cases.

In another three cases subsegments showed isolated emphysema (Figure I); in these the appropriate bronchus was ectatic.

On the other hand, in 20 to 30 cases, emphysematous secondary lobules were seen singly or in numbers scattered in random fashion throughout the lungs, frequently related on one or more sides to macroscopically normal lung. The bronchioles supplying the affected lobules were usually seen to be irregularly dilated, and the residual strands of lung tissue in the affected part were generally relatively coarse. Where there was no definitely visible interlobular septum the borders of the affected lobules were less clearly demarcated from the normal lung (Figure II).

(*b*) *Lesions Apparently Unrelated to Anatomical Units*

Examples apparently unrelated to anatomical units were very commonly found and include such frequently observed forms of emphysema as those occurring around scars and the large air spaces referred to as bullæ. Although close examination frequently reveals evidence that anatomical units were originally involved, this is obscured by the deformation of lung tissue produced by scarring and the large air spaces, sufficiently to distinguish this group from that preceding.

The term "scar" applied to the lung requires amplification. It should not infer a purely fibrotic lesion but rather a condensation of lung tissue in which there is a very variable degree of chronic inflammation. Readily seen scars show ectatic bronchioles, or even bronchi, entering their substance, so that such areas represent the *residuum* of a once much larger volume of lung tissue (Laennec, 1834).

Most such scars show emphysema of variable degree immediately related to them. Loeschcke (1928) illustrates this point well. In the present series the clearest examples of this type of emphysema were found surrounding tiny (two to four millimetres) calcified tuberculous foci such as are commonly found in the lung parenchyma. In cases in which the "scar" was extensive, that is, in chronically collapsed segments or lobes, such emphysematous change can be seen in adjacent segments or even in the adjoining part of the adjacent lobe (Figure III).

A scar can often be found at one or both lung apices. Their reported incidence varies greatly, depending on the author's criteria of definition of a scar (Moore, 1951). Bunting (1942) describes the variants of the apical scar adequately and notes that it is frequently surrounded by a zone of emphysema.

A localized fibrotic condensation of lung tissue, often showing thickening of the overlying pleura, of sufficient size to be seen clearly macroscopically and outlined on its deep surface by a recognizable zone of emphysema, was present in 75% of unselected "normal" cases. Most frequently the emphysema was minimal, but many showed small air cysts beneath the scar. Some cases showed a patch of small cysts subpleurally below which a plaque of scar could be felt (Figure IV). A small number showed large air cysts superficial to the scar.

These larger air cysts are usually termed bullæ or, less often, tension cysts, as their distended appearance suggests a high internal pressure (Figure VIII).

Small isolated bullæ or tension cysts were occasionally seen in the parenchyma of otherwise normal lungs varying from 0·5 centimetre diameter to a maximum of 2·0 centimetres diameter. Occasionally, tiny scars were seen related to the proximal surface of the cyst. When multiple, as in one of these cases, the condition resembles that which is usually described as a type of "congenital cystic lung", frequently regarded as a separate pathological entity. Since most authors now regard "congenital cystic lung" as a condition acquired after birth (Dickson, Clagett and

FIGURE III

Localized emphysema. An old tuberculous infection has resulted in collapse and fibrosis of the subapical segment. The adjacent part of the lower lobe shows considerable emphysema. The interlobar pleural space has been obliterated by the inflammatory process. (Slightly reduced)

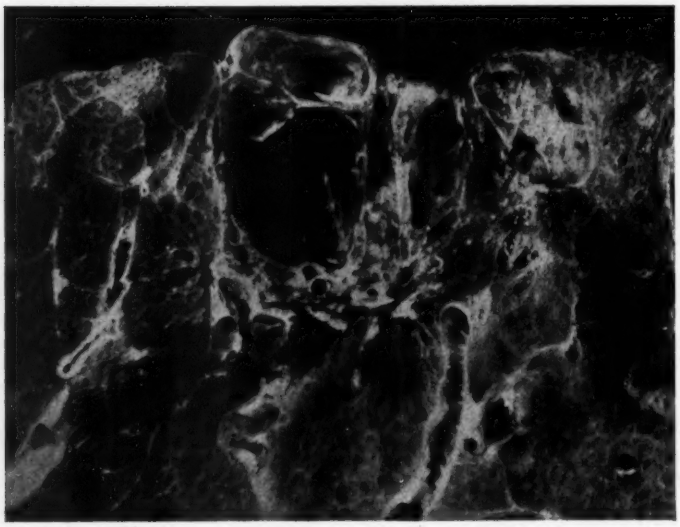

FIGURE IV

Localized emphysema. An irregular group of small cysts is situated immediately distal to a dense " scar " at the apex of the lung. The subapical segment (on the left) is only slightly involved. (×4)

McDonald, 1946; Caffey, 1940), this term should fade into desuetude.

Subpleural cysts of a similar size are, if anything, commoner, but, whereas there is apparently an upper limit of about 2·0 centimetres diameter of the size of cysts surrounded by lung tissue, cysts related to the pleura are frequently relatively huge. The largest in this series was 10 centimetres in diameter and therefore must have almost filled one hæmithorax (Figure V). These large cysts were usually seen at the apex of the lung but were found occasionally elsewhere. One unusual solitary cyst 8·0 centimetres in diameter arose from the centre of the diaphragmatic surface of the lower lobe. Regardless of site, such cysts regularly show some scarring at their base.

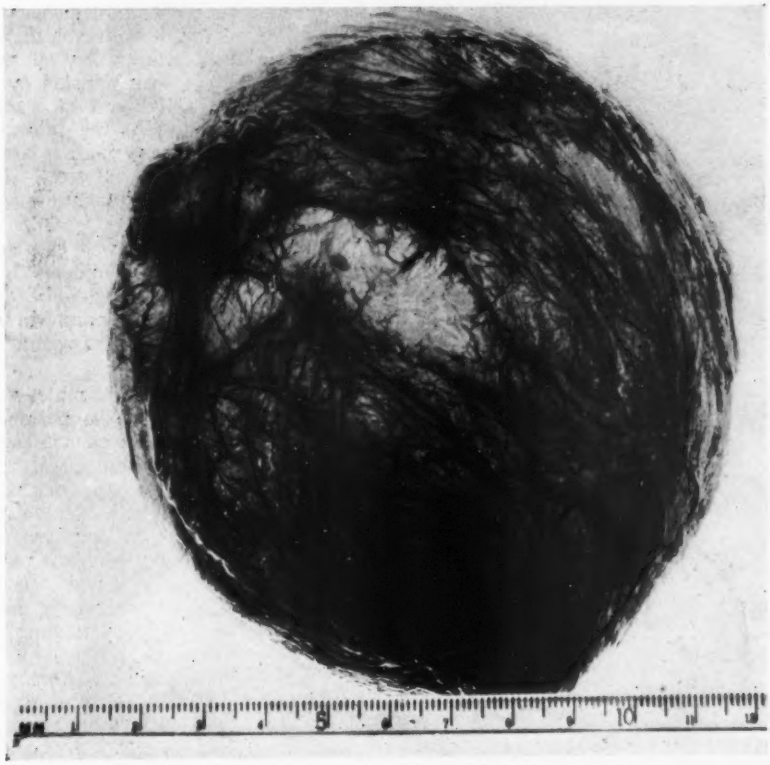

FIGURE V

Localized emphysema. A large subpleural bulla 10 centimetres in diameter, removed at operation. The vascular network is prominent

One uncommon form of localized emphysema, not clearly involving anatomical units, is that seen extending over large areas of immediately subpleural tissue, the remainder of the parenchyma being normal. One such case was described by Loeschcke (1928) as unique in his experience. In the present series there have been three cases in which this change was noted. Two showed a rim of bronchiolectasis and slight emphysema 1·0 to 2·0 centimetres in width lying subpleurally, sharply segregated from the normal lung beneath. In one lung the subpleural tissue related to the heart was involved and in the other, that related to diaphragmatic surfaces of the lower lobes. The remaining case showed gross generalized subpleural bullæ with the underlying lung exhibiting only slight emphysema (Figure VI). This variant is relatively rare and macroscopically is distinct from the commoner forms.

(*2a*) Generalized Emphysema Without Localized Accentuation (89 Cases)

Emphysema affecting every segment and showing in overall pattern is common enough in its pure forms. Gough (1952) divided the generalized disease into two types, focal or centrilobular, and a less distinctly orientated form showing maximal change on the periphery

FIGURE VI

Localized emphysema. This section through an upper lobe shows numerous subpleural bullæ, the underlying lung being nearly normal. All the other lobes were similarly affected by this unusual process. (Approx. ×0·5)

of lung units. This classification has been followed by Heppleston (1947, 1953, 1954). The second type has been termed "diffuse generalized emphysema" in this paper.

(i) *Focal (Centrilobular) Generalized Emphysema*

Focal (centrilobular) generalized emphysema was well illustrated by Loeschcke (1928). Gough (1940) suggested the name "focal" applied to examples occurring in coal-trimmers.

All grades of severity of this form have been observed. If all these grades are included, the group constitutes by far the commonest form of generalized emphysema. If cases with small areas of local emphysema superadded are included a total of 52 cases have been examined. In those autopsies performed at random, the majority of male patients over fifty-five years of age showed this change, usually of minor degree.

The earliest lesions showed slight dilatation of the air passages in the middle of the secondary lobules (Figure VII). Lesions vary from this size to 6·0 or 7·0 millimetres in diameter, with occasional larger areas many of which have the appearance of early tension cysts (Figure VIII). A variable amount of black pigment can be seen related to the broncho-vascular branches in the emphysematous areas as well as that in the more usual sites—subpleurally and in the septa, particularly adjacent to the veins.

General inspection showed the lesion to be roughly similar in development in different parts of a particular lung. The distribution of the lesions was relatively uniform throughout the lung with no definite exaggeration in size in any one area.

The large majority of examples was seen at a stage where most of the peripheral tissue in the secondary lobules was unaffected (Figure VIII). Only in one instance were the lesions gross enough to affect all the lung parenchyma and still retain a recognizable focal pattern. Some of the cases of focal emphysema, particularly two with virtually no black pigmentation and with well-developed centrilobular emphysema, form a group which also could be described as "congenital cystic lung".

(ii) *Diffuse Generalized Emphysema*

The pure form of generalized diffuse emphysema constitutes the classical emphysema described in most textbooks (Dible and Davie, 1950; Moore, 1951; Muir, 1951). In its pure form it was not commonly found, nine cases only fitting the criteria.

These nine cases showed the whole lung affected by a generalized dilatation of air spaces. In two examples this was almost completely uniform throughout the lung (Figure IX), and corresponded to the description of Crenshaw and Rowles (1952) of "cotton-candy lung".

The remainder showed the emphysema more advanced on the periphery of lung units, with the formation of confluent air spaces subpleurally, along septa, bronchi and blood vessels, as described by Gough (1952). The whole process of emphysematous change was

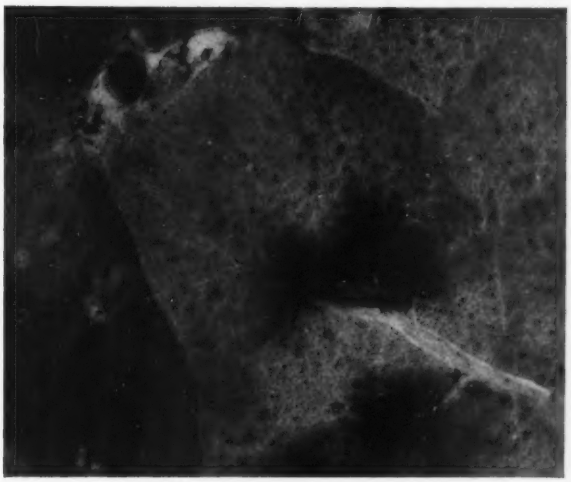

FIGURE VII

Generalized focal emphysema. A secondary lobule occupies most of the picture. The dark area seen centrally surrounding the bronchiolar and pulmonary arterial branches is due to early emphysema. Granular deposits of black pigment are visible around the radicals, as well as in the interlobular septa related to the vein above. (×4)

FIGURE VIII

Generalized focal emphysema. The lesions are more advanced than that in Figure VII and show clearly as emphysematous spaces. The " focus " below is typical, whereas that above is macroscopically identical with an isolated " tension cyst ". The parenchyma on the periphery of the lobules is not affected by emphysema. The " foci " contain a minimal amount of black pigment. (×4)

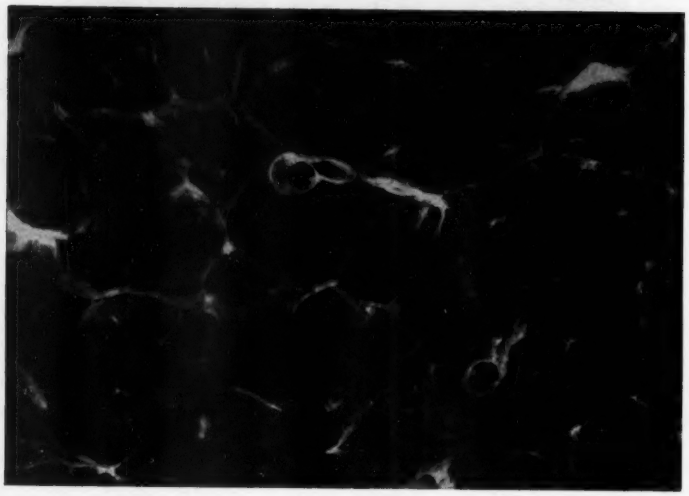

FIGURE IX

Generalized diffuse emphysema. The preparation is a wet mount of a 600μ section cut by the large section technique. The whole lung was affected by emphysema of the type illustrated (compare with Figure X, which is of the same magnification). The prominent structures centrally and the lower right are irregularly dilated bronchioles. (×4)

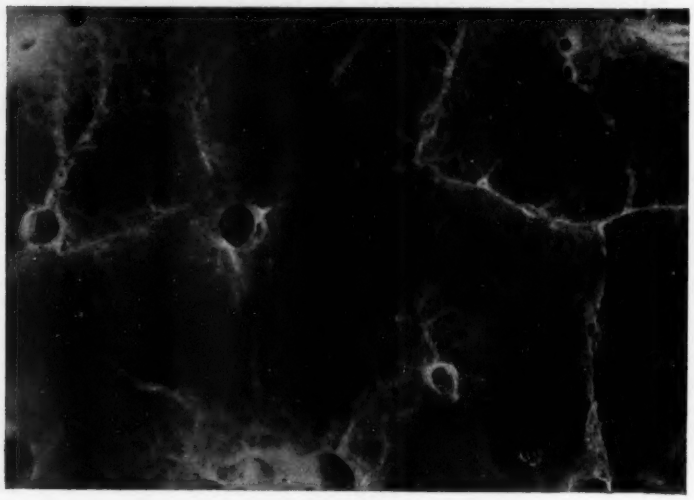

FIGURE X

Generalized diffuse emphysema. The pattern of the emphysema is just recognizable as centrilobular, particularly to the upper right. Centrally the areas are becoming confluent with disappearance of interlobular septa, leaving a network of fine residual strands (the darker, more regular tubes are vessels, distended by intravenous fixation). (×4)

generally more advanced in the lingula and middle lobe and to a lesser extent in the true upper lobes; the lower lobes showed the least change.

In all cases the air cysts rarely exceeded 1·0 centimetre in diameter and the residual strands of lung tissue were very fine.

No early case of diffuse generalized emphysema was seen; only well-developed lesions were observed.

On the other hand 28 cases showed mixtures of focal and diffuse emphysema. The diffuse emphysema was of two kinds, the first showing fine strands of tissue as in the type described above. Those with minimal diffuse emphysema generally showed this change at the periphery of the lung, with focal emphysema elsewhere. Most often the diffuse change occurs towards the tip of the middle lobe and lingula and, in more progressively advanced cases, shows the change of the whole of the middle lobe and lingula, the pectoral segment of the upper lobe and the remaining segments of the upper lobe, in that order. The focal emphysema associated with this type is not generally advanced beyond the relatively early stages (Figure X).

The second type of diffuse change seen in association with focal emphysema shows coarser strands and relatively larger confluent air spaces. The associated focal emphysema is usually also more advanced. The minimal lesions appeared to occur by confluence of areas of focal emphysema often seen first in the middle of lung segments (which are, in the upper lobe, approximately 3·0 centimetres from the pleura). This change was seen most frequently in the true upper lobes, but also in the middle lobe and lingula and (particularly posteriorly and at the apex) in the lower lobes (Figure XI).

More advanced lesions show confluent air spaces over large areas of the lung toward the periphery, the lung adjacent to the pleura and intersegmental septa being the last to be involved (Figure XI).

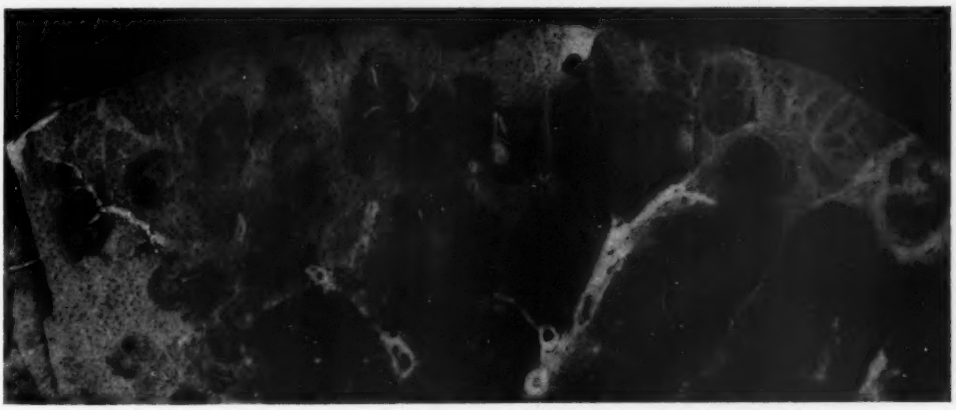

FIGURE XI

Generalized diffuse emphysema. Sagittal section through the upper lobe, showing the posterior part. To the left, classical focal emphysema can be seen. Centrally these areas have become confluent, particularly deep in the lung. To the right the thicker septa alone are undestroyed, but less affected tissue can be seen immediately beneath the pleura. (Natural size)

Finally, in the severest lesions, either with the emphysematous process involving these areas or with apparent compression of them, the emphysema occupied a large volume subpleurally with ragged strands running from the parenchyma below to the pleura. Intersegmental septa disappear and free communication exists between segments (Figure XII). Extensive degrees of this form of emphysema were not seen, presumably because such are incompatible with life.

(2*b*) GENERALIZED EMPHYSEMA WITH LOCALIZED ACCENTUATION (30 Cases)

Cases of generalized emphysema with minor apical lesions have been included in the previous group. More extensive changes of a local nature were found in approximately 30 cases.

(i) *Multiple Local Lesions*

The emphysema in five cases could be seen clearly to consist of multiple local lesions, there being completely normal lung units remaining in a scattered fashion throughout the lung (Figure XIII). These cases showed emphysema in lobules or groups of lobules, the bronchioles of which were severely damaged and often ectatic. Many more cases could have been assigned to this group, particularly those in which there was a long history of asthma, but the appearance in them was not as clear cut.

(ii) *Generalized Emphysema with Superimposed Localized Emphysema*

Twelve cases showed generalized emphysema with superimposed localized emphysema very well; a few showed grossly emphysematous segments, subsegments and lobules in a lung with only moderate change elsewhere. Other lungs with variable degrees of localized emphysema had large bullæ arising from scarred areas at the apex, or increase in the process around scars.

When specimens are examined from this point of view, most cases of advanced emphysema show some variation in the extent of the process between lobules and segments.

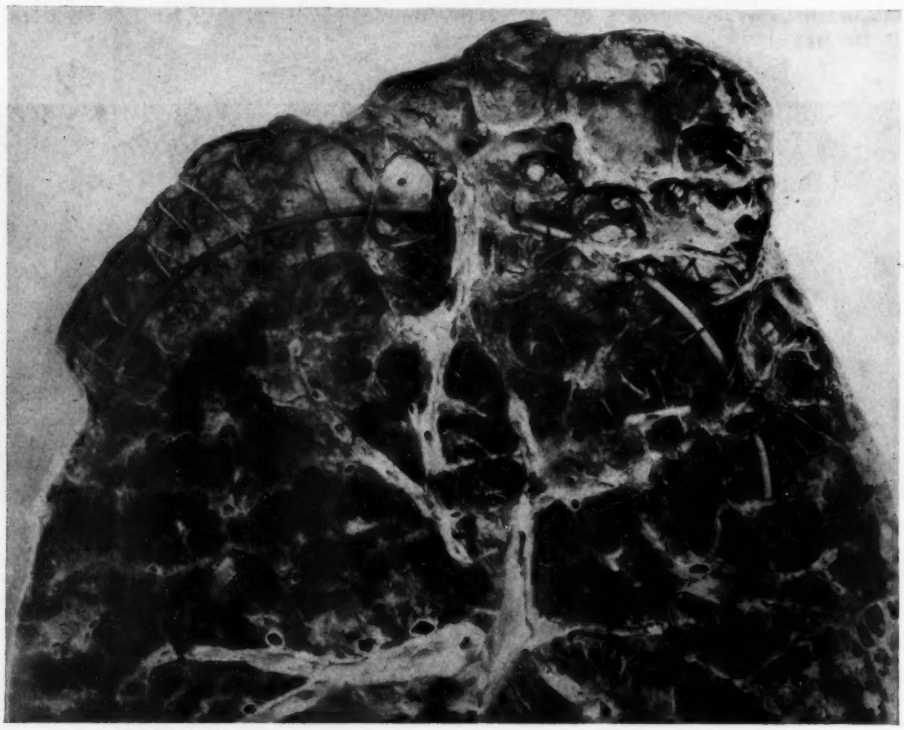

FIGURE XII

Generalized diffuse emphysema. Sagittal section through the upper lobe. The pattern of focal emphysema can be recognized to the lower left. The remainder of the lung was similarly affected. Elsewhere in the illustration the emphysema has become confluent and thick septa, even of intersegmental size, have been disrupted. A plastic tube demonstrates the continuity of the air spaces. A rim of condensed lung tissue is visible on the lower right. (Slightly reduced)

ASSOCIATED PATHOLOGY

(1) *Inflammatory Lesions*

Macroscopic features of inflammatory changes are always present in emphysematous lungs. Some of these observations have already been mentioned briefly. They will be presented under these headings: (*a*) lesions in the bronchial tree; (*b*) lesions in the lung parenchyma; (*c*) pleural lesions.

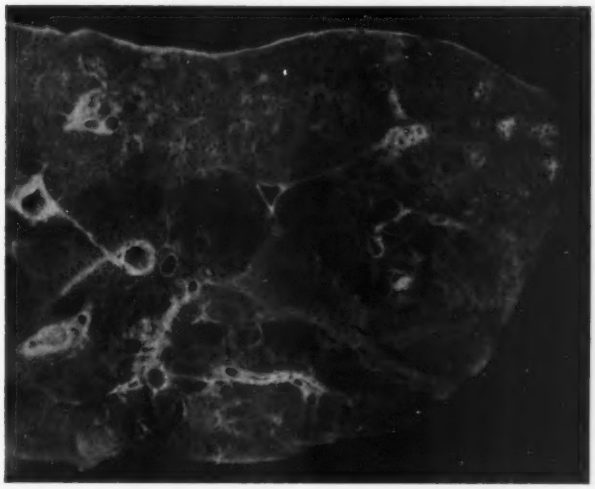

FIGURE XIII

Generalized emphysema with localized accentuation. Both lungs were affected in the same manner as the area illustrated, with the appropriate bronchioles showing bronchiolectasis. Much of the lung shows a terminal acute bronchiolitis, seen as small white areas in the non-emphysematous lung in the upper part of the illustration. (×3)

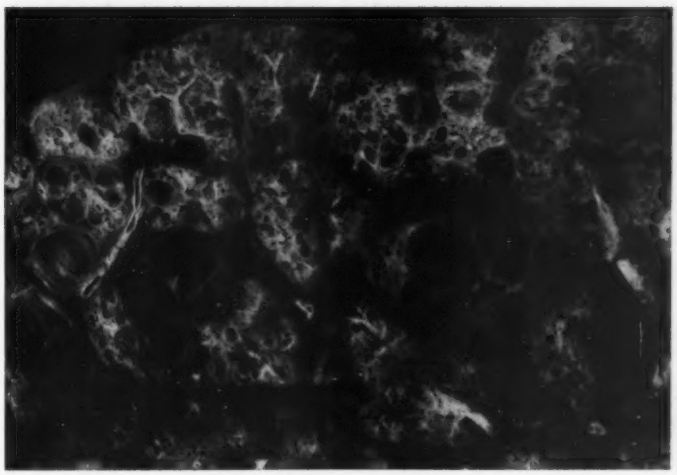

FIGURE XIV

"Pulmonary fibrosis." The dark amorphous bands separating the areas of emphysema are masses of condensed lung tissue showing considerable fibrosis. Much of both lungs was similarly affected. (×4)

Lesions in the Bronchial Tree. Acute tracheobronchitis and acute bronchiolitis was readily recognizable in the large majority of advanced cases and was usually considered clinically to be the precipitating cause of death (Figure XIII).

Lesions of presumably longer duration included bronchiolectasis and bronchiectasis. Bronchiolectasis could be recognized readily in practically all the cases of both localized emphysema and advanced generalized emphysema; particular care was required in preparation of specimens and in examination to see this change convincingly in less advanced generalized disease, but some ectatic bronchioles could be recognized in these lungs, most bronchioles not showing definite change.

Bronchiectasis was recognized less often. Gross saccular bronchiectasis was not seen in emphysematous areas. Moderately dilated bronchi were often recognizable in gross generalized emphysema and were regularly seen where a lung unit of subsegmental size or larger was affected by localized emphysema.

Lesions in the Lung Parenchyma. Bronchopneumonia of variable extent was commonly seen in cases in which terminal infection in the bronchial tree was evident. The relation of the area of consolidation to the bronchioles is frequently difficult to discern in advanced generalized emphysema. In the focal lesion, acute inflammatory exudate in the centrilobular area was the form observed.

The close anatomical relation of pulmonary scars to areas of emphysema has already been emphasized. This relation is more clearly seen in localized than in generalized emphysema.

In a group of 11 cases scarring was very extensive throughout the lungs, with a variable degree of emphysema. Three showed the typical changes of silicosis and two were recognizable histologically as tuberculous in origin. The remainder were regarded as nonspecific (Figure IV). This group is generally separated from generalized emphysema and is then termed " pulmonary fibrosis ". However, many grades intermediate between classical generalized emphysema and extreme pulmonary fibrosis were noted.

Distinct from the group in which pulmonary scars were seen, six cases showed the yellowish consolidation of chronic pneumonia (Kaufmann, 1929) involving areas of segmental size or larger.

Pleural Lesions. Acute inflammation of the pleura was not observed commonly. Extensive lesions were seen in only three cases, one of which was associated with an empyema. Pleural adhesions, on the other hand, were often observed, particularly associated with extensive apical lesions and with advanced generalized disease. Occasionally pleural thickening was seen and was extensive in two cases. Adhesions, on the other hand, were not common (about 10%) in cases of focal emphysema with or without early diffuse change.

The observation of Ameuille *et alii* (1937) and of Korol (1938) that bulla formation is never advanced beneath extensive areas of adhesions was confirmed.

(2) *Pulmonary Pigmentation*

Black pigment is commonly found in non-emphysematous lungs, particularly in elderly subjects. Near the hilum large amounts may be seen in the lymph nodes. Peripherally the pigment is obvious subpleurally, often outlining lobules and in the septal interstitial tissue, being most densely aggregated near tributaries of the pulmonary veins. Smaller amounts of pigment can usually be seen around the broncho-vascular radicals in the middle of the lobule.

In the focal form of diffuse emphysema these black pigment granules around the broncho-vascular radicals are more easily seen. In many cases the amount of pigment in the " focus " was in excess of that seen in unaffected lungs, but the amount visible varied greatly not only from lung to lung but from focus to focus. The degree to which the focal emphysema had developed was not related to the amount of pigment; cases showing all grades of focal emphysema were encountered in which there were insignificant amounts of pigment.

These observations are not in accord with those of Heppleston (1947, 1953 and 1954) who has studied the morphology of focal emphysema in coal-workers. He concluded that the coal dust in the " focus " has a primary role in the pathogenesis of the lesion.

Both the mining and industrial or domestic use of black coal in this state are limited. Only two of the patients found to have focal emphysema in this study had worked with black coal for any length of time, yet the incidence of focal emphysema in the adult male population was found to be extremely high.

Therefore it can be concluded that the typical lesion commonly develops in the absence of coal dust, an observation made by Gough (1952), and that exposure to coal dust or even to dusty atmospheres is not essential in the pathogenesis of focal emphysema.

Similarly, although emphysema of most other types showed general increase in the

amount of black pigment in the lung parenchyma, a few examples of each type were encountered in which there was insignificant pigmentation. One exception to this rule was those cases of severe generalized emphysema of the fine strand type (" cotton-candy lung "). Characteristically, in these there was strikingly little pigmentation of the remaining parenchyma (Figure IX), an observation recorded long ago by Ohkubo (1908).

CONCLUSIONS

A number of limited conclusions can be drawn from the observations presented.

(1) *The Nature of Pulmonary Emphysema*

The macroscopic characters of localized and generalized emphysema have much in common. It seems likely that, first, any satisfactory hypothesis of ætiology should be capable of explaining both types, and secondly, that the basic phenomenon responsible for the development of emphysema should be found in the lung. These rather obvious conclusions are drawn because many hypotheses, such as that of the primary effect of kyphosis (Kountz and Alexander, 1934), ignore them.

The constant association of the disease with evidence of chronic inflammatory changes in the lung requires explanation. From macroscopic appearances alone it is impossible to conclude whether the inflammatory changes are primary or secondary.

Emphysema so frequently occurs either purely locally or in a pattern having " local sign " that it seems probable that the basic lesion, if such exists, is locally acting and that generalized forms are due to the generalized occurrence of this local lesion.

(2) *The Evolution of Generalized Emphysema*

The arrangement of generalized emphysema into types and the severity of lesion has, inherent in it, suggestions regarding the evolution of the disease.

A minority of cases of generalized disease appear to arise by occurrence of a sequence of local lesions (Group 3*a*). The majority suggests that a gradually (but not necessarily continuously), progressive generalized pattern evolves. The following scheme is offered.

The earliest recognizable lesions in generalized emphysema are focal or centrilobular. In the majority of cases this progresses to easily recognized emphysema. A relatively small number of these progress further, retaining the focal pattern, and some cases of generalized diffuse emphysema affecting the whole lung can be regarded as the extreme forms of this type. Considerably more often, progress of the disease obscures the centrilobular pattern.

In some cases, at a stage when the dilatation of the centrilobular area has advanced to a relatively minor extent, diffuse fine emphysema begins at the periphery of the lung. This progresses most frequently from the middle lobe or lingula to the pectoral segments of the upper lobe, involving all the lung parenchyma of these units relatively uniformly, but showing most change at the periphery of lung units. Possibly this form may progress to diffuse fine generalized emphysema affecting the whole lung, but this is not common.

Other cases show diffuse emphysematous change at a later stage of development of focal emphysema. This change consists in the fusion of areas of focal emphysema maximal in the spatial centre of lung segments or subsegments, that is, near the periphery of the lung. Lung tissue either related to intersegmental septa or immediately subpleural is usually affected last. The gross forms show partial destruction of intersegmental septa with the result that gross subpleural emphysema develops. Coarse strands run from the pleura to the underlying lung, which always shows well developed focal emphysema.

These remarks apply to the pure forms of generalized emphysema. Most cases departing from this pattern show a local lesion or lesions which can be recognized to be similar in nature to the pure localized lesions described in Group (1).

(3) *The Evolution of Localized Emphysema*

A pattern of change similar to that described for generalized emphysema has not been clearly observed. The reason for this is felt to be associated with the relative severity of the bronchiolar and parenchymal changes which so distort the normal anatomy. If these changes are assumed to be primary, then the suggestion could be made that more extensive local lesions are required to produce emphysema in a normal lung than in a lung which is more uniformly affected by the process.

SUMMARY

The macroscopic morphology of 180 cases showing the variants and degrees of pulmonary emphysema is presented. The classification of the types is purely descriptive and terms containing ætiological preconceptions have been avoided.

A study of the gross morphology of the disease demonstrates that the generalized forms

of the disease can be reasonably regarded as multiple and confluent local lesions. This emphasizes the essentially pulmonary nature of the disease (from the ætiological point of view) and demands a further and closer study of the (preferably early) local lesions or of specific areas in generalized lesions.

The early (and thus particularly significant) lesions occupy a constant and characteristic position in the lobules of the lung.

ACKNOWLEDGEMENTS

My thanks are due to the cooperation of the staffs of the Departments of Morbid Anatomy of the Royal Melbourne, Alfred and St. Vincent's Hospitals, and to the Honorary Staff of the Royal Melbourne Hospital for access to their records.

This work was carried out during the tenure of a grant from the National Health and Medical Research Council.

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PARIETAL LOBE SYNDROMES[1]

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. . . To one person, the clinical picture may appear as a straight-forward dementia: to another, it may seem that the inadequate performance is the outcome of an agnosia (or apraxia, or aphasia). The manner of carrying out a prescribed task, the behaviour in a given test situation, may be so similar both in the case of the dement and in the patient with a small and circumscribed parietal lesion that there is room for a legitimate difference of opinion. Indeed an over-confident judgement is only too often the mark of inexperience.

—MACDONALD CRITCHLEY (1953)

Though isolated observations on symptoms resulting from parietal lobe lesions were reported in the last century, the majority of detailed studies date from the last fifty years, and seem to have lagged behind the elucidation of functional localization in other parts of the cortex. This delay would seem to be due to the fact that parietal lobe function cannot be studied from animal experiments, with the result that we have to rely almost exclusively on clinical observations compared with pathologically verified lesions.

The traumatic experiences of the first World War, utilized by Head and Holmes, Dejerine, and Goldstein among many other British and Continental neurologists, mark the first great advances, and Goldstein and Gelb's (1918) famous patient, Schn., reported in 1918, has been the subject of repeated studies and heated arguments up to the present.

With Gerstmann's (1924) communication concerning a woman with a combination of finger agnosia, right-left disorientation, acalculia and pure agraphia, began the next chapter of parietal symptomatology, and several further reports on related subjects appeared from the Viennese school led by Poetzl in the succeeding years.

During the second World War, Bender in the United States of America paid detailed attention to higher level visual defects following on parieto-occipital injury. Critchley has published a series of papers concerning the various aspects of parietal lobe disturbances over the past seventeen years, culminating in the publication of his book "The Parietal Lobes" in 1953. The selective bibliography of this book cites 1093 references, a striking indication of the worldwide interest this subject has aroused in neurological and psychiatric circles.

ANATOMICAL DEFINITION

The anatomical boundaries of the parietal lobe are purely arbitrary and empirical, and likewise from the functional point of view no definite borders can be defined. The sum total of neuro-physiological, clinical and pathological evidence during the last two decades has shown beyond reasonable doubt that the earlier concepts of a functional correlation with the cyto-architectonic mosaic of Campbell, the Vogts and Brodmann are no longer tenable. These histological methods had indicated that certain areas of the cortex might have predominantly sensory and others primarily motor functions, but beyond that they have no definite functional correlates. The cyto-architectonic maps of forty years ago have erroneously lulled us into a false concept of minute cortical localization.

The origin of efferent projection pathways from the parietal lobe contributing a considerable proportion of pyramidal fibres, as shown by Lassek and others, and the extensive thalamo-cortical connexions to the frontal lobe demonstrated by Le Gros Clark and Walker, revealed that even the fissure of Rolando was not a strict division between motor and sensory functions, and so we came to speak of a sensory-motor cortex which included both the frontal and the parietal lobes.

If we remember the extensive systems of association fibres linking the different cortical regions, and even uniting the two hemispheres via the *corpus callosum*, we can appreciate that disturbances similar to those resulting from parietal lobe disease have also occurred in lesions of the temporal and frontal regions.

[1] Received on January 23, 1956. Read at a meeting of the Section of Neurology and Psychiatry, Australasian Medical Congress (British Medical Association), Ninth Session, Sydney, August 20 to 27, 1955.

Of considerable significance are the studies in comparative anatomy showing that the parietal lobes and frontal association areas increase in size and volume much more than other cortical regions as we ascend the phylogenetic scale, and reach their maximum development in man. This would point to the importance of these areas for higher gnostic and intellectual functions.

The critical observations of Goldstein and of Critchley of the immense variety of disturbances of symbolic thought and language in patients with parietal lobe disease leave little room for any materialistic concept of specific cortical speech centres, and Head's suggestion of a semantic, syntactic and nominal aphasia related to narrow cortical zones can no longer be accepted. The more dynamic view of the Gestaltists, first suggested by Hughlings Jackson almost forty years before its Continental exponents, regards the cortex as an integral unit, and pays due consideration to the functional capabilities of the remaining healthy regions rather than stressing purely the disturbances from diseased areas.

The different clinical manifestations resulting from lesions of the dominant and subordinate hemisphere have been known to us for a long time; yet so far no histological difference between the two hemispheres has ever been demonstrated. The recent observations on the results of hemispherectomy have modified even our old-established ideas of cerebral dominance, and would point to some interdependence between the two hemispheres or some biparietal integrative function.

In this connexion, the clinical assessment of left-handed patients with parietal lobe lesions has shown that there is not a simple reversal of dominance of the hemispheres, and that the problem of sinistrality seems much more complicated than was once imagined.

From all these considerations it would appear that the title of "parietal lobe syndromes" cannot be taken as anatomically accurate, but that we are here concerned with symptoms of disease only predominantly involving the arbitrary boundaries of the parietal lobe, and not infrequently extending into the posterior temporal and occipital regions.

We should also not be tempted to confuse the signs of disease of a particular area of the brain, such as the parietal lobe, with the normal function of this area. Abnormal signs are not infrequently release phenomena, representing the activity either of some other region of the nervous system or of the parietal area proper released by a lesion at some different site.

Clinical Presentation of Parietal Lobe Lesions

As the parietal lobes stand so high in the evolutionary scale and their connexions with other cortical and sub-cortical structures are complex and wide, the manifestations of disease of these regions might be expected to be anything but simple. The clinical consequences are diverse, ranging from slight disturbances, detectable only by special methods of examination, to serious failures of several facets of higher gnostic functions. These clinical signs do not depend only on the site of the lesion, but are determined also by its size, abruptness of onset, rate of growth or progress, duration of clinical history, and not least by the type of brain in which the disease process occurs: the patient's pre-morbid personality, his intellectual standing and his adjustment to his environment.

The stage at which the patient is first examined is of considerable importance, as in ischæmic cerebral vascular disease the earliest manifestations may be focused on the parietal lobes, with a gradual spread of the pathological process over the years to involve the other association areas and produce the clinical picture of dementia.

Any rigid classification of parietal signs into syndromes of an assumed focal lesion thus becomes virtually impossible, and we can only speak of certain combinations of clinical symptoms and signs which are suggestive, though not always diagnostic, of disease of the parietal lobes.

Within these limitations, some clinical manifestations may occur in lesions of either hemisphere, while certain parietal syndromes seem to be specifically associated with disease of the dominant or of the subordinate side, and others are found most frequently in bilateral lesions.

Critchley, with due warning about the dangers of systematization, has drawn up schemata of the characteristic clinical disorders specifically associated with disease of each of the two hemispheres, and has discussed the difficulties arising in the supposed reversal of dominance in left-handed persons.

This small series of 14 cases may illustrate some of these points, though I must admit at this stage that local circumstances did not permit the exhaustive special tests and detailed investigations of parietal lobe disturbances achieved by English and Continental neurologists. As these tests are time-consuming and often require special techniques, they cannot always be performed in the consulting room, and are difficult to fit into the rush of a general hospital, where beds are always scarce.

Lesions Involving the Left (Dominant) Hemisphere in Right-handed Persons

Eight patients of this series presented with symptoms suggestive of disease of the dominant parietal lobe; they are all right-handed. In one the lesion was proved to be a malignant glioma, in another it was of the nature of cerebral atrophy, while the remaining six patients are all presumed to suffer from cerebral vascular disease affecting the left parietal lobe, though no pathological proof is available. Four of these patients may be discussed in some detail.

CASE 569, N.N.C.—A clerk, aged sixty-three years, had an episode of temporary loss of memory and disorientation followed by a blackout in 1950, and during the succeeding two years had two or three similar blackouts, lasting one-half to one minute only, and not interfering with his work. In September, 1952, he gradually became dysphasic and found it progressively more difficult to express his thoughts in words. In the course of his work as a clerk on the Sydney Harbour Bridge it was found that he could no longer add figures or even assess the toll to be paid by cars passing through the gate, although he had been doing this work for over twenty years. Within the next few weeks he lost his ability to write and had a further three blackouts suggestive of epileptiform seizures, though without focal features. His family had not observed that he had any difficulty in dressing himself or finding his way about in his home. The patient was, however, completely unaware of any disturbance in his health. He walked into the room with the greeting: "How are you, doctor? I hope you are well; I am very well." (Anosognosia.) He was well orientated in time and place, but at first was unable to state his address. He had a severe aphasia, which was mainly of the expressive type; when shown a pencil, cigarette lighter or match he could not name any of them, but knew exactly what they were used for and, for instance, to the pencil or pen remarked: "To write with." He had considerable difficulty in distinguishing between his right and left hand, and responded very slowly when asked to touch his left ear with the right index finger. While he was able to write his name correctly, he could not spell the street he lives in, and when asked to write down the Lord's Prayer, he failed miserably; he therefore had considerable dysgraphia. He was quite unable to draw a house, a daisy or a bicycle (constructional apraxia). He could not even add 2 and 3, but on two occasions gave a correct answer when asked for the toll for a motor-car with two or three passengers crossing the Sydney Harbour Bridge. (The toll is 3d. for each passenger and an extra 3d. for the car.) When asked for the toll for more than three passengers, he failed again, though he had been doing this work for many years (acalculia). Finger agnosia was not specifically looked for in this patient.

On routine neurological examination slight weakness of the right side of the face and right hand and arm was found, and the tendon reflexes in the right upper limb were a little brisker than those on the left. While there was no impairment of cutaneous sensation to single stimuli, nor even astereognosis, he would neglect a painful stimulus on the right hand when both hands were simultaneously touched with a pin (tactile inattention). There was no defect of the visual field, but special tests for higher visual functions, such as visual disorientation, were not carried out. X-ray, electroencephalographic and cerebro-spinal fluid examinations suggested a space-occupying lesion in the left lower parietal region, and burr-hole biopsy confirmed this to be of the nature of a glioma. A portion of the tumour was excised, but the patient died some six months after this operation.

In summary, then, this patient presented with anosognosia, dysphasia, tactile inattention and constructional apraxia, as well as Gerstmann's syndrome.

CASE 48, G.S.—A second patient was found to have an almost pure Gerstmann's syndrome when first examined in 1953, but over the next two years developed signs of more extensive cerebral vascular disease. She was a housewife, aged fifty-seven years, who complained of some deterioration of memory, fatigue, and occasional headaches. She herself was rather unconcerned about these symptoms and relied mostly on her sister to relate her history. Though the patient seemed to be almost unaware of these disabilities, her sister had noted a gradual deterioration of her writing and spelling, progressing to a stage where she was no longer able to prepare a shopping list. At the same time she was found to make many mistakes when paying for groceries, and had to rely on her friends or relatives to check the change. These disabilities seem to have been noted by her closest relatives only, and she was still able to attend social gatherings and lead an active life in church affairs. She was well orientated in both time and place, knew about most current events, but showed some deterioration of recent memory. She had definite finger agnosia, and was quite unable to point to either her own or the examiner's index and middle fingers when asked to do so. There was severe right-left disorientation, which included both her own anatomy and that of the examiner. While she was still able to sign her name, she failed with her address, and could write neither spontaneously nor to dictation; she was, however, able to copy words written down for her in block letters (Figure I). Acalculia was confirmed by her failure to add even the simplest sums, and when asked for the cost of two threepenny ice-creams she replied: "Threepence."

This combination of finger agnosia, right-left disorientation, dysgraphia and dyscalculia comprises the four cardinal manifestations of Gerstmann's syndrome. In addition to this, this woman could not even draw a semblance of a daisy, house or clock, as shown in Figures I and II (constructional apraxia). While there was no apparent difficulty with the verbal expression of her thoughts or with the understanding of spoken symbols, she had a dyslexic type of aphasia. When shown the word "thunder" she read, after a long while, "the other", and when shown the word "scientific", she could not read it at all. There was, however, no defect in her visual acuity or in the visual fields on repeated perimetric examinations over several months. Routine neurological examination revealed no disturbance in the cranial nerves, in motor or sensory functions, or in the reflexes. The cardiovascular system appeared to be clinically normal, and the blood pressure was 140 millimetres of mercury (systolic) and 100 millimetres (diastolic). X-ray examination of the skull and air encephalography revealed no abnormality, and the cerebro-spinal fluid was normal in all respects. The electroencephalogram, however, contained some low-voltage slow waves in the left parieto-temporal region, which did not progress significantly during the succeeding two years.

When this woman was examined again two years after the onset of her symptoms, the parietal signs

remained practically unchanged, but further deterioration of her memory had occurred, suggesting a more general cerebral vascular impairment. She was examined on seven occasions during these two years, and there was a striking variability in her performance of specific tasks at different times. In general, her defects were much more apparent in unaccustomed surroundings, or particularly in front of an audience when she was presented at a lecture-demonstration.

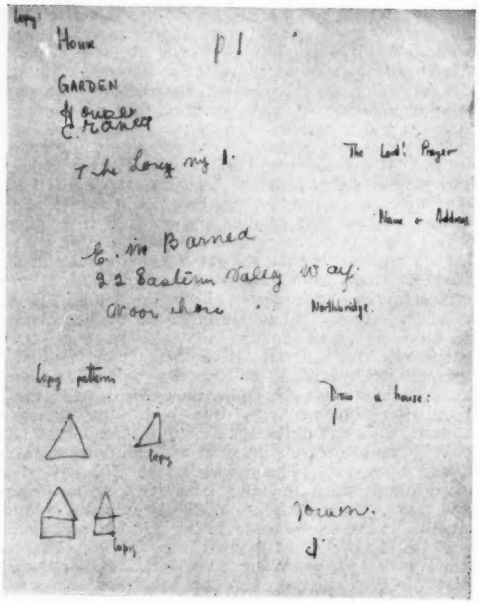

FIGURE I

Case 48, G.S., showing dysgraphia, inability to draw, and inaccuracy in copying patterns

However, even during a single examination she would occasionally make a gross error one moment and give a successful response to a similar question a few minutes later. When asked to write she was very slow, hesitated before each letter, and then often changed her mind and either crossed out or erased what she had written. This variability of performance is another feature of patients with parietal lobe disease, first noted by Head and Holmes.

CASE 2250, N.N.C.—The third patient, a man, aged forty-five years, was referred by an ophthalmic surgeon because of a right hemianopia. He was brought by his sister, as he was quite unaware of any illness and, indeed, refused to admit to any disturbance of his health, and particularly vision, even on specific examination. His sister informed us that his vision had been failing for some three years, though he could not be induced to consult a doctor about this. In December, 1954, he became very depressed and irritable, and was finally taken to a physician, who had him admitted to a mental hospital for shock treatment. This was fortunately withheld, and he was discharged after some five weeks, with the remark that he would be fit to return to his work. His early personal history had a strong psychiatric flavour; he was spoilt by his parents, frequently played truant, and never passed any of his State examinations. After leaving school he could not settle down to any job, relied on his parents for financial support, and often spent all his belongings on alcohol. During his Army service he had a reputation for petty thieving, and after his discharge remained unable to settle in any occupation. In 1952 his friends began to note a gradual deterioration. He started to repeat his words, and later also his actions, and would wind the clock over and over again at night. His language grew sparse, and he relied on fewer and fewer words, mostly monosyllables. He withdrew more and more into himself, would not do anything on his own initiative and refused to return to work. In 1954 visual disturbances were first observed by his relatives; he would move about slowly in his home, and feel his way as he went along, often knocking over things

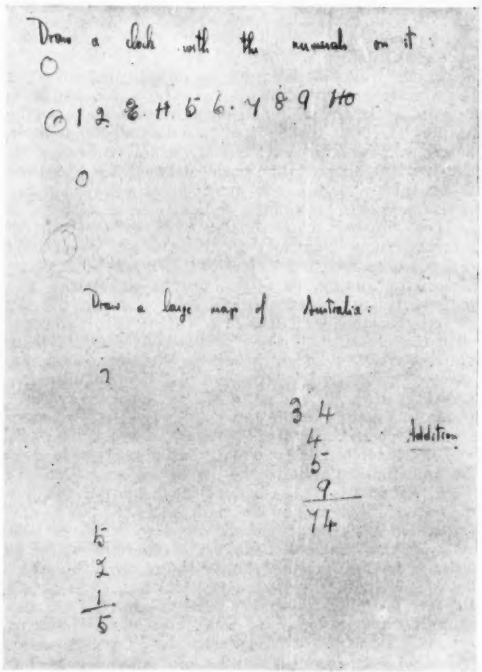

FIGURE II

Case 48, G.S., showing patient's attempt to draw a clock, and to add simple sums

accidentally. When trying to do a small repair job on a bicycle, he put the nut some two inches away from the bolt.

When the patient was questioned, he had no idea why he should have come to see a doctor, suspected that he might have had "a nervous breakdown". When asked where he came from, he said "Hamilton, in Hamilton, County of Newcastle", though correctly Hamilton is a suburb of the City of Newcastle. At times he appeared to be confused, while at others he answered questions well and was able to carry on a reasonable conversation. He repeatedly refused to

admit to any visual failing, though it was obvious either that there was a gross reduction of his visual acuity, or that he was unable to understand what he saw.

The visual acuity of the right eye was 6/18 and that of the left 6/12. There was a homonymous right hemianopia, and the peripheral part of the left field seemed to be restricted. His ability to see and distinguish objects varied considerably during repeated examinations; at times he was quite unable to tell where the examiner was in the room, and found much difficulty in distinguishing shapes and forms; at others he could see and name small objects quite distinctly, and was able to read simple words, though he failed with the more complicated and unaccustomed expressions. He did not seem to be aware of the nearness or farness of objects shown him, but detailed tests for visual disorientation and tachistoscopic examinations were not carried out. He had a complete Gerstmann's syndrome, and Figures III and IV show his attempts at writing his name and address, and drawing a house, a face and a daisy. It is rather

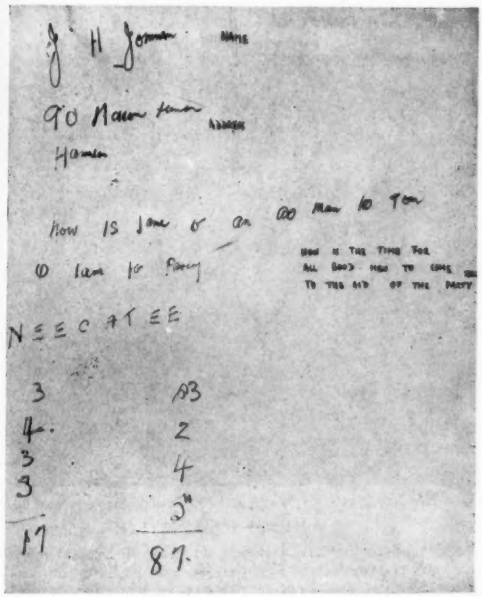

FIGURE III

Case 2250, N.N.C., showing marked dysgraphia and acalculia

significant on Figure IV that the drawing occupies only the left half of the page, the right side being completely neglected. This neglect of the right visual field cannot be explained alone by his hemianopia, as it is well known that patients with a pure visual field defect can usually compensate for this by movement of the eyes or head.

He was unable to find his nose, eye or ear when asked to do so (autotopagnosia), but must have understood the question, as he had no difficulty in pointing to the examiner's nose, ear or eye. There was, however, no indication of dysphasia, and he was quite able to understand all that was said to him, name objects shown to him, as far as vision permitted, and in most instances express his thoughts adequately. Apart from tactile inattention over the right limbs there was no sensory impairment, and even two-point discrimination and stereognosis were normal. No other abnormality was found on full neurological examination.

The electroencephalogram revealed a flattening of the electrical rhythm in the left parietal region and some slow-wave activity in the left mid-temporal

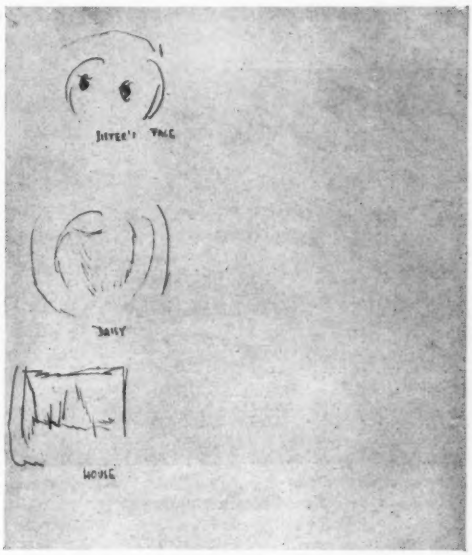

FIGURE IV

Case 2250, N.N.C.: attempts at drawing a face, daisy and house. Note the complete neglect of the right half of the paper

area. An air encephalogram showed mild general cerebral atrophy with gross atrophy of the left parieto-occipital lobes as indicated by a pronounced dilatation of the posterior horn of the left lateral ventricle (Figures V and VI). The cerebro-spinal fluid was normal; it did not react to the Wassermann test.

This patient, then, had a radiologically proven lesion of the left parieto-occipital area, and in addition to a Gerstmann's syndrome presented with visual agnosia and autotopagnosia.

In the remaining five cases of this group of dominant hemisphere lesions, the ætiology was thought to be vascular; the ages of the patients ranged from fifty-eight to sixty-four years. The abrupt onset of symptoms in all of them, without loss of consciousness, suggested a thrombotic episode. One patient only was examined within three days of the onset of his illness; in the other four cases, the initial vascular accident had occurred from six months to five years before I first examined the patients.

While all five gave a history of weakness of the right arm or of right hemiplegia at the onset of their illness, residual signs of minimal weakness of the right hand were found in only two.

One patient (Case 184, G.S.) related that his right arm and right leg suddenly became quite numb and dead: "I could not feel them at all, and thought that I had lost my right limbs." However, his wife mentioned that there was no obvious paralysis of these limbs,

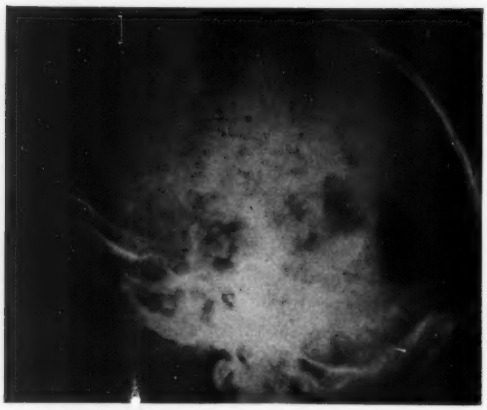

FIGURE V

Air encephalogram from Case 2250, N.N.C., showing gross dilatation of the left occipital horn in the lateral view

and he had no objective loss of strength when examined some nine months after this incident, though he was still severely dysphasic.

This phenomenon of neglect, or reluctance to use the affected limb, although objective loss of power or coordination is only minimal, was observed in two other patients, and is quite characteristic of parietal lobe disease. It indicates, of course, the importance of parietal integrity in the awareness of the body image.

Two of these patients had an objective sensory loss consisting of hypoalgesia, impaired two-point discrimination and astereognosis on the affected side, and in one tactile inattention was found without any other sensory impairment.

All five patients were dysphasic; in three the difficulty was mainly one of expression, while in the other two the understanding of spoken speech as well as the expression of their thoughts was severely impaired.

CASE 555, G.S.—A rather unusual disturbance of language occurred in a woman, aged fifty-eight years. She had suffered from severe hypertension for over ten years, and had a complete heart block with occasional Stokes-Adams attacks. At the age of fifty-three years she had suffered a sudden right hemiplegia with a complete loss of speech which persisted for two months. After this a few words returned gradually, and she became able to express her thoughts in simple sentences, but would repeat the last word of each sentence over and over again. When she was examined some five years after the onset of her illness, her vocabulary was very limited, and her sentences were made up of only three or four words with an invariable repetition of the last word, such as: "Dr. A. is very bad, bad, bad, bad. Dr. B. wonderful man, man, man, man." Her family thought that she was making up the number of words she wanted to say by repeating the same word several times. She retained a reasonable understanding of the spoken word and could follow simple commands, but was quite unable to read. In addition to a slight residual right hemiparesis, she neglected the right half of her body, and also exhibited some autotopagnosia.

FIGURE VI

Antero-posterior projection of air encephalogram from the same patient as in Figure V, confirming the marked dilatation of the posterior parts of the left lateral ventricle

This repetition of the last word of a sentence is not very common in aphasics, and I am not certain whether it represents a type of palilalia or an automatic echolalia. Palilalia is usually associated with diffuse pallido-striatal disease, of which there was no evidence in this patient. On the other hand, she did not exhibit any spontaneous echolalia—that is, repetition of words said to her—at the time of my examination.

All five patients had a dyslexic type of aphasia, though four of them could read simple

words, stumbling only over the more complicated and unfamiliar symbols.

A complete Gerstmann's syndrome was found in three patients. One patient had only right-left disorientation and dysgraphia without finger agnosia or loss of mathematical ability, and in the fifth the dysphasia and mental deterioration were too severe to permit adequate examination.

Constructional apraxia, revealed by an inability to draw simple objects or arrange Koh's blocks according to sample patterns, was found in the four patients who could be tested for this.

While none of these five patients had defects in the visual field demonstrable by perimetry, attention defects in the right visual field were found in two on simultaneous bilateral stimulation. More specific tests for higher visual functions, such as unilateral visual disorientation, were unfortunately not performed.

Autotopagnosia, or an inability to point out various parts of the patient's own anatomy, was found in three of these cases, and in one was confined to the affected right half of the body, which she generally neglected.

In summary, the symptomatology of these patients included the following features: (i) Mild loss of power of one or both right limbs, accentuated by a more characteristic neglect of the affected limbs. (ii) Objective sensory impairment, particularly in regard to discriminative and localizatory sensory functions such as two-point discrimination and stereognosis. (iii) Tactile inattention over the affected limbs, even if superficial sensation was otherwise intact. (iv) Defects in the visual fields and more particularly attention defects on bilateral simultaneous stimulation. (v) Constructional apraxia, which is essentially a disorder of spatial thought. All these disturbances may occur in disease of either the dominant or the subordinate parietal lobe, though constructional apraxia is described as being more common in lesions of the non-dominant side. In addition to these disorders, we have described defects more specifically associated with disease of the dominant hemisphere, including the following: (vi) Dysphasias of infinite variety—and, indeed, no two patients with dysphasic disturbances are ever exactly alike. (vii) Dyslexia. (viii) Gerstmann's syndrome. (ix) Visual autotopagnosia.

Some of the other manifestations described in association with disease of the dominant parietal lobe, such as bilateral ideokinetic apraxia, pain asymboly, spontaneous turning around a vertical axis and Schilder's syndrome (motor aphasia, apraxia, universal hypalgesia, pathological laughter) were not encountered in this small series.

Lesions Involving the Right (Subordinate) Hemisphere in Right-handed Persons

Four patients complained of symptoms suggestive of involvement of the subordinate parietal lobe; they were all right-handed. In two, the pathological process was neoplastic, in one, most probably traumatic, and in the fourth, vascular.

CASE 1561, N.N.C.—A man, aged forty-three years, was referred for investigation by a psychiatric clinic. He had a bad background, including several terms in gaol for thieving, and a long history of alcoholism with frequent head injuries during alcoholic brawls. At the age of forty-one years he began to suffer from epileptiform fits, and some six months later developed a headache which progressively increased in severity. He was moderately confused, and seemed to be quite unaware of an unsteadiness of his gait which was obvious to the examiner. He admitted that he had been unable to control his bladder for some time, but showed no concern over this. He was neglected in his appearance, and was stated to have been unable to care for himself. He was dull, retarded and apathetic.

During the examination it was quite obvious that he neglected the left half of his own body as well as the left half of his environment or extra-personal space. There was, however, no right-left disorientation. He was able to sign his name, though rather inaccurately with some difficulty, and when asked to write or draw, consistently neglected the left half of the paper. He was quite unable to copy patterns of triangles built with matches, and could not even attempt to draw a flower or a house. He succeeded with simple calculations, such as multiplying 2 by 3, but did not persevere when asked to calculate the cost of four beers at 10d. each. There was no impairment of his language, and he was able to understand the spoken word and express his thoughts adequately. However, he had considerable difficulty in dressing himself (dressing apraxia), and particularly neglected again the left half of his body. Figure VII shows his neglect of the left half of the paper and constructional apraxia.

The visual fields could be tested only by confrontation, and revealed an attention defect in the left field. There was very slight hemiparesis, but considerable increase of the tendon reflexes on the left side, and the left plantar response was extensor. Although he was able to feel touch and pinprick over the left limbs, he neglected the left-sided stimulus completely when both sides were stimulated simultaneously. While there was no evidence of cerebellar defect or posterior column loss, he was quite ataxic, used small steps and dragged the left leg. This may represent a pseudo-cerebellar ataxia described in parietal lesions of either hemisphere, but in this patient a peripheral contribution from his chronic alcoholism could not be excluded.

Papillœdema suggested a space-occupying lesion, and this was supported by the electroencephalogram, which revealed a slow-wave focus in the right parieto-temporal region. A right common carotid angiogram

indicated a large space-occupying lesion in the right posterior temporo-parietal region. This patient died a few weeks after this, and autopsy confirmed the presence of a large right parietal glioma.

CASE 797, N.N.C.—Another patient deserves detailed mention because of his rather unusual visual manifestations. He is a man of thirty years, who was first examined in January, 1953. He had suffered from nocturnal epileptiform seizures for the preceding

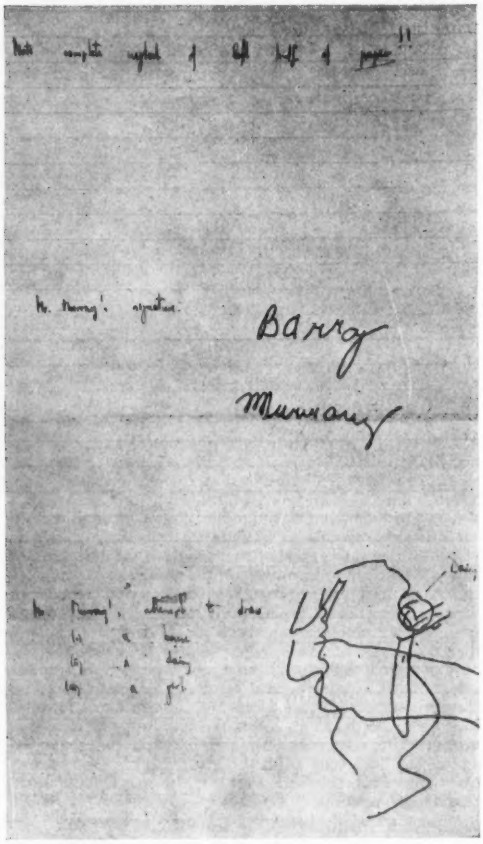

FIGURE VII

Case 1561, N.N.C., showing patient's irregular handwriting, and attempts to draw a house and a daisy. Note that the objects drawn are superimposed, and that the patient completely neglects the left half of the paper

three months. One morning in September, 1952, he was reading the paper when the print suddenly seemed to blur; he put the paper down, but was still able to see the print on the wall in front of him. Since then similar attacks of visual perseveration recurred almost daily, and were usually worse on any emotional excitement. He said that after looking at people he would retain an after-image of them which persisted, even when he shut his eyes, for several minutes. While he was on holidays in a country town, all the people on the street suddenly seemed queer to him; their arms and legs on the left side suddenly assumed an odd shape and seemed to shake. He said to his wife: "Aren't the people queer shaped; one arm is fat, the other thin, and one side of their face is fat, the other thin." He also thought his wife all out of shape, and said to her: "Look how big your feet are." These episodes of metamorphopsia persisted for two minutes at a time, and recurred on several occasions during the succeeding weeks. On one occasion when he was shopping with his wife, he remarked after another woman had left the shop: "I can still see that lady standing there, although I know she has gone out." During 1953 he had momentary episodes when coloured objects would suddenly appear spontaneously in his left visual field; during these episodes he appeared absent and became moderately dysphasic, saying only simple words indistinctly and very softly, though he appeared to understand what was said to him. They lasted for some five to ten minutes. On one occasion, after seeing a "Technicolour" film, he complained that the impression of the colours persevered for several hours after he had left the theatre.

Almost simultaneously with these symptoms he also noticed a difficulty in hearing sounds from a distance beyond five yards; conversation then seemed to him jumbled and unclear, though he could hear quite distinctly from close up. He then noticed that, like visual impulses, sounds would also perseverate after he had heard them. As an example, after turning off the radio, he would usually hear the last few words or sentences or bars of a musical item over and over again for several minutes. This was most noticeable with radio programmes, and was not specifically reported in regard to conversation of friends addressing him. This auditory perseveration persisted during the succeeding seven months, and was reported repeatedly during progress examinations. In August, 1953, he had several episodes of visual hallucinations, in which he saw coloured circles on the walls and on different objects in the room, which appeared to be moving from the right to the left; these were followed by major epileptiform convulsions.

There was no obvious dysphasia, no dyspraxia and no neglect of the left half of his body or left extrapersonal space. On perimetric examination a partial homonymous left lower quadrantic defect was found. The only other abnormality on neurological examination was a slight weakness and clumsiness of the left hand, but there were no reflex changes and no sensory impairment. The electroencephalogram revealed a slow-wave focus in the right temporo-occipital region, which progressively deteriorated on repeated examinations. The cerebro-spinal fluid was normal in all respects, but a right common carotid angiogram demonstrated an abnormal vascular pattern in the posterior parietal region, and on air encephalography there was an encroachment on the occipital horn of the right lateral ventricle which filled incompletely. The patient refused to go into hospital for surgical treatment, and unfortunately more detailed tests of his higher visual functions were impossible, as he had moved to another town and failed to attend for further examinations.

The outstanding manifestations of parietal lobe disease in this case were visual perseveration, metamorphopsia and auditory perseveration. The visual phenomena persevered in time, and to this condition the term paliopsia

has been applied; it may occur in lesions of either hemisphere. Metamorphopsia—that is, an illusory distortion of objects—like the paliopsia was of episodic occurrence, and involved either the right half of the visual field or on one occasion both sides. In this case it was essentially an alteration in the size of objects and a distortion of their shape; the objects appeared strange and queer, and in general rather ugly. Metamorphopsia again may occur in disease of either parieto-occipital region, and has also been described in diffuse cerebral disorders, in psychoses, and particularly in toxic states, such as mescal and hashish intoxication. The unformed visual hallucinations preceding this patient's epileptiform seizures are, of course, not uncommon in focal parieto-occipital lesions. The auditory perseveration reported by this patient seems to be a rare phenomenon, and as far as I am aware has not so far been reported in the literature.

CASE 698, G.S.—A third patient in this group, a housewife, aged sixty years, sustained a head injury in which she struck the back of the right side of her head on the floor. She was not rendered unconscious, but has little recollection of the events of the next three days. She then became aware that she was unable to tell the time; although she could see the figures on the clock, she could not interpret them. When trying to call a friend on the telephone, she found that she could not use the dial. She was able to ascertain the time from the wireless, but could not set her clock because she had no idea of where to put the hands. Although she stated that she could see clearly, she tended to bump into objects on her left. She also mentioned a difficulty with reading; she could see the words clearly enough, but could not follow the lines and would often read the same line over and over again. Her husband had noticed that she would miss the plate when pouring milk into her porridge, and related with some mirth that she had considerable difficulty with dressing herself, and would put her pyjama trousers on back to front. She had also some difficulty finding her way about the house, and on one occasion had to call for her husband's help as she could not find her way back from the bathroom. There was no dysphasia, and no weakness or unsteadiness of her limbs. She had no dysgraphia, but when she attempted to draw a clock face, she reversed the numerals, and in her drawing of a house, the left wall is completely omitted; when she drew a map of Australia, she left out the western cities (Figures VIII, IX and X).

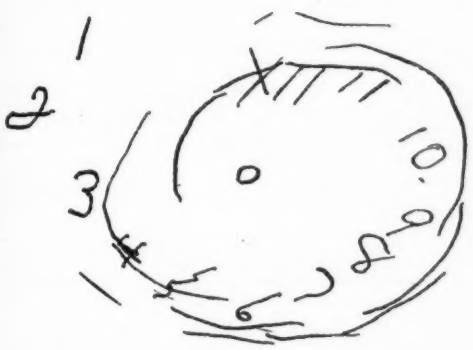

FIGURE VIII

When the patient in Case 698, G.S., attempted to draw a clock, she reversed the numerals

FIGURE IX

Drawing of a house by patient in Case 698, G.S., in which she omitted the left wall

On perimetric examination a complete homonymous left inferior quadrantic defect was found, but there was no other abnormality on routine neurological examination. Her blood pressure was raised to 200 millimetres of mercury, systolic, and 120 millimetres, diastolic, and one can therefore not be certain whether her illness was traumatic or vascular in nature. The cerebro-spinal fluid was entirely normal, and the electroencephalogram revealed only a higher amplitude of a normal α rhythm in the right hemisphere. Five weeks after the onset of this illness this woman had recovered from all her symptoms, and even the visual field improved.

The significant parietal lobe symptoms in this case include a pronounced neglect of the left half of the extra-personal space, a dressing apraxia and a partial failure to understand written symbols which found its expression particularly in an inability to tell the time. She also had a transient dyslexia, which could not be explained only by the partial defect of her visual fields.

CASE 20, G.S.—The last patient in this group was a hypertensive woman, aged thirty-eight years, who had suffered from a severe right cerebral vascular accident with unconsciousness lasting for several weeks; it was thought that this was of the nature of a cerebral hæmorrhage. She was first examined twelve months after this incident, when she had complete left homonymous hemianopia and spastic left hemiplegia, as well as severe sensory loss over the left half of her body. The remarkable feature in this woman was that she thought she had a supernumerary or phantom third hand on the left side, and she referred to this hand as "Rufus". Rufus was not always present, but at times was imagined most vividly, and thought to be slightly smaller than her normal right hand. It seemed to assume unusual postures, and often felt as if it were in contact with her chest. It was never painful and she gradually came to accept this phantom, was even amused by it, and discussed it quite frankly.

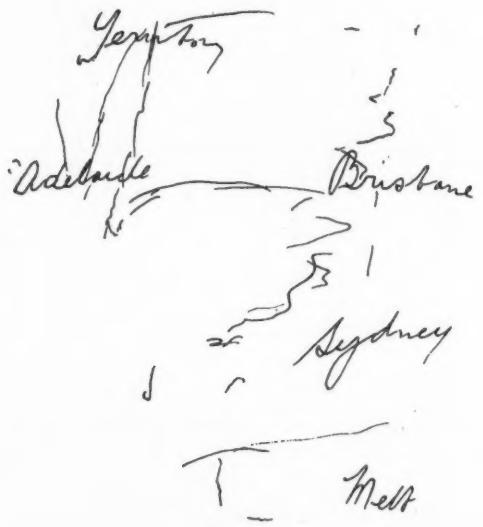

FIGURE X

Drawing of a map of Australia by patient in Case 698, G.S., with complete neglect of the western cities—that is, the left half of the map

This is, of course, again a disorder of the body image or a paraschematic lesion which has been described in association with disease of the subordinate parietal lobe.

In summary, the specific disturbances of subordinate parietal lobe function in these four patients included the following: (i) disorders of the body image, either a neglect of the affected left half of the body or a phantom third limb on the affected side; (ii) a neglect of the extra-personal space, particularly of its left half; (iii) anosognosia or unawareness of disease, in one patient only.

The tactile inattention, constructional apraxia, visual perseveration and metamorphopsia may occur in lesions of either hemisphere, as was mentioned earlier.

Bilateral Parietal Lesions

Two of my patients were thought to suffer from disease of both parietal lobes, and the history of their illness suggested a vascular ætiology in both.

CASE 432, G.S.—A commercial traveller, aged sixty years, was unaware that there was anything wrong with him, and could not understand why he should be in hospital. However, his family had noted during the preceding eighteen months that his memory was impaired, and his efficiency at his work had deteriorated so much that he lost a position which he had held for many years. Though he would not admit to this, his family reported some paranoid ideas, particularly a feeling that his fellow employees were all against him.

On examination of the patient, a severe impairment of recent memory was apparent, though he stoutly denied this. There was no dysphasia, and he was able to read, but it was doubtful whether he understood all he read. He had severe dysgraphia, and was unable even to copy words, and he had an acalculia. However, there was no finger agnosia or right-left disorientation. He was unable to draw even a semblance of a house or a flower, but managed a clock face in a somewhat irregular fashion. There were no significant abnormalities on routine neurological examination, but he had signs of peripheral vascular degeneration. The cerebro-spinal fluid was normal, but the electroencephalogram showed bilateral slow waves suggestive of diffuse cerebral disease.

The clinical picture pointed to diffuse cerebral vascular disease rather than pre-senile dementia, and the signs of parietal lobe involvement were the complete anosognosia, severe constructional apraxia, acalculia and dysgraphia. There was no obvious evidence of visual disorientation, but the patient could be examined only in bed, and specific tests were not carried out.

CASE 136, G.S.—The last case is of some interest in regard to the problem of dysphasia; it concerns a man, aged seventy-three years, who had held a responsible position as a head brewer until the age of sixty-nine years. At the age of seventy years a gradual impairment of memory became apparent and progressed. After some twelve months he first found some difficulty in expressing his thoughts, and at the same time his writing deteriorated, and his reading became progressively slower. At the age of seventy-two he was still able to read the destination signs on a tram, and could go into town one day a week to meet his friends without losing his way. Gradually his condition deteriorated, and a few months before I examined him he was found wandering on the streets, unable to find his way home. When I first examined him he had lost all ability to read or write, though he could still copy his signature. He could feed himself, but often confused his utensils, and would, for example, use a spoon for a fork. There was some dressing apraxia, and his wife had observed him putting his trousers on over his pyjama pants. However, there was no right-left disorientation.

He appeared to be unable to understand what was said to him, but had some spontaneous speech, which

was distinctly pronounced. However, he frequently had difficulty in finding the exact word he wanted to say, and then would invariably make this up with the word " faka ", which seemed to serve him as a sort of universal substitute for all the words he could not find. His sentences were usually quite simple and often recurring, such as " How are you today ? " and he could not name objects shown to him. The remarkable feature in this patient was that he could still play the piano, either from memory or from musical scores placed in front of him. A variety of scores were handed to him, ranging from cow-boy tunes and folk songs to classical music, and he invariably played them correctly, though he would occasionally miss the key and then continue playing the whole piece in the wrong key. Even when shown music outside his own collection and probably unknown to him, he was still able to play it correctly. If his wife hummed a tune he could improvise the accompaniment to this on the piano. His wife related that he often spent hours at the piano and enjoyed this immensely.

Routine neurological examination revealed no abnormality, but adequate sensory testing or examination of the visual fields was impossible because of his dysphasia. His personal habits and behaviour at home were beyond reproach, and there were no clinical indications of primary dementia, though the patient was first examined almost three years after the onset of his symptoms.

This patient had, therefore, lost his understanding of spoken and written symbols, but retained the ability to read musical symbols and understand the musical sounds he heard. On the expressive side, while there was a severe disturbance of speech, musical expression remained, both spontaneously and in response to visual and auditory musical perceptions.

Cases have been reported in which aphasics retain the ability to sing the words of a song or hymn and would join in a chorus. Alajouanine (1948) recorded the classical case of Ravel, who developed severe mixed aphasia after a cerebral vascular accident, but was still able to recognize tunes and appreciate that a piano was out of tune ; he was, however, unable to read music. His expressive musical ability was severely impaired. He could play scales only and had lost his power of composition and orchestration. It would seem that in the majority of aphasic patients musical ability is also lost, and amusia may occur at times even without other aphasic disturbances.

The symptoms of visual disorientation and constructional apraxia which are described as occurring in their severest forms in bilateral lesions of the parietal lobe could not be elicited in these patients because of their inability to cooperate adequately in specific tests.

CONCLUSION

Although but few in this small series of patients were subjected to the exhaustive variety of special tests required to study every aspect of parietal lobe disorder, it should be apparent from their complex and varied symptomatology that no territory within the brain surpasses the parietal lobe in the rich variegation of clinical phenomena which follow disease states. It must also be stressed that the majority of the clinical manifestations suggestive of involvement of the parietal lobes are rarely complained of by the patient, and will be missed unless they are specifically looked for. I realize with regret the higher visual disturbances I must have overlooked in some of my patients because I was not experienced in the methods of testing for them.

It should now be apparent how difficult it may be to distinguish the gnostic disturbances of a patient with a parietal lobe disorder from a global dementia. Dementia, by definition, refers to a deterioration in intellectual capacity which is irreversible. Incongruous or anti-social conduct, mood changes inappropriate to the occasion, disorientation of time and place, ignorance of current events and severe impairment of memory, regressive signs in the nervous system and an inability to deal with new and unfamiliar problems generally point to more diffuse cerebral involvement—that is, dementia. Disorders of language, dyspraxia, gnostic disturbances in visual perception and a patchy loss of specific intellectual abilities with other faculties and behaviour apparently unaffected would suggest a more focal lesion. However, no hard and fast rule is possible, and it is well known that even a circumscribed lesion can at times produce a global dementia.

It is not unexpected that many of these patients may at first sight be labelled hysterics, and the anosognosia of a person suffering from disease of his parietal lobes can easily be confused with the " *belle indifférence* " of the hysteric. Again, the variability of performance observed in parietal lobe disorders is not unlike the variation of clinical signs in hysterics. However, while the hysteric remains blissfully indifferent to his failures in a specific task, the patient with organic disease frequently responds with a catastrophic reaction, or else tries to avoid or bypass his disabilities by various trick manœuvres.

These points can only serve as guides in distinguishing agnosic affections from psychiatric states. The final decision, as in other aspects of clinical medicine, will always depend on a careful clinical assessment of the individual patient.

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THE MORPHOLOGICAL STUDY OF VARIOUS LESIONS OF SKELETAL MUSCLE[1]

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Sydney

THE reaction of muscle to disease is imperfectly understood, and it is with this study that the present paper is concerned. The following account is based on a personal examination of a large amount of material collected in the Department of Pathology of the University of Leeds. The lesions in the tongue are discussed separately.

PHYSICAL INJURY

Mechanical Injury

The early stages of regeneration of striated muscle after operative incision were studied in 17 subjects who had died at periods ranging from one to fifteen days after operation. In another group of 18 cases, the material examined included old surgical operation wounds and injuries of muscle produced by bruising, fracture of bone and extraneous foreign substances.

Recent Injuries.—At the end of one day after operative incision, examination of the immediate vicinity of the wound shows necrosis of the muscle fibres with loss of striation and disappearance of the nuclei. There is an infiltration of polymorphonuclear leucocytes, and sometimes there are much œdema and hæmorrhage in the necrotic tissue. The muscle fibres for a short distance from the necrotic zone are separated from one another by œdema and inflammatory cells; and isolated fibres show hyaline degeneration or necrosis.

After three days there is early invasion and phagocytosis of some of the necrotic fibres by histiocytes, and a few fibroblasts are also present in the œdematous endomysium.

Five days after operation the cellular infiltration contains many histiocytes and fibroblasts. There is no evidence of regeneration of the injured muscle fibres, even at the end of six days.

After seven days there are early signs of muscular regeneration. New buds sprout from the stumps of the preexisting muscle fibres and extend for a short distance into the fibroblastic tissue which has formed. By the tenth day regeneration has proceeded a little further. In places, the newly-formed fibres terminate as multinucleated bulbous masses, and sometimes these appear in a single section as isolated giant cells in the fibroblastic stroma. There are no mitoses.

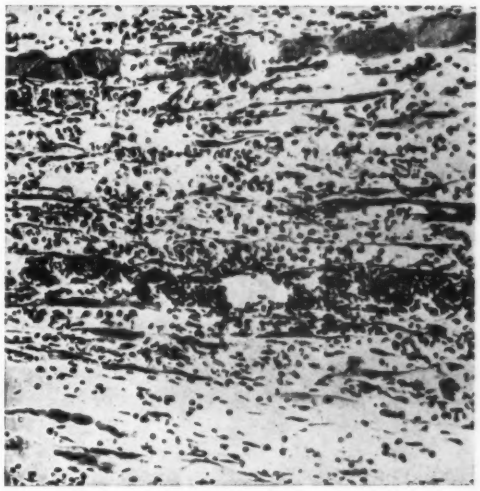

FIGURE I

Section through a human limb muscle following mechanical injury, to show fine strands of regenerating fibres in the endomysial tubes. The latter contain many histiocytes and much blood. (×145)

At the end of fifteen days the site of injury is occupied by dense fibrous tissue, and there are few regenerating muscle fibres.

One case deserves special mention (Figures I and II). In this instance muscular regeneration was well advanced and was apparently related to the preservation of the original fascicular pattern and to the relative absence of fibrous tissue between the individual muscle fibres. Some of the fibres in these areas showed degenerative changes; others were

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necrotic and were invaded by histiocytes; and in many places there were endomysial tubes lined by fibroblasts and containing histiocytes and fragmented muscle tissue. Newly-formed muscle fibres were growing freely in these tubes. Somewhat similar appearances have been observed in my experimental study of the regeneration of skeletal muscle (Constance, 1955).

Old Scars in Muscle.—Histologically the most pronounced feature in old injuries is the presence of dense fibrous tissue which has replaced the muscle to a greater or lesser degree. There is atrophy of the muscle fibres in the fibrotic areas, and in some lesions the atrophic

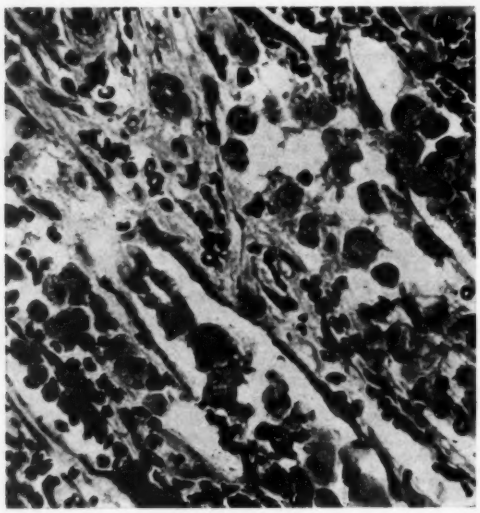

FIGURE II

Endomysial tubes with numerous histiocytes. There is phagocytosis of the necrotic muscle fibres. Same case as Figure I. (×336)

muscle cells contain many nuclei and appear as multinucleated elements. The cross striations, however, are well preserved in most of these fibres. In a few cases degenerative changes are also present in the muscle involved in the scar. In several instances foreign-body giant cells are observed in relation to particulate matter which is usually a relic of suture materials.

Signs of regeneration of the injured muscle tissues are seen in five of the post-operative cases. The change often consists of the development on the ends of the old fibres of multinucleated plasmodial outgrowths of sarcoplasm which grow into the fibrous tissue for a very short distance.

Effects of Radiation on Skeletal Muscle

The various changes in the muscle which are observed after therapeutic irradiation are often

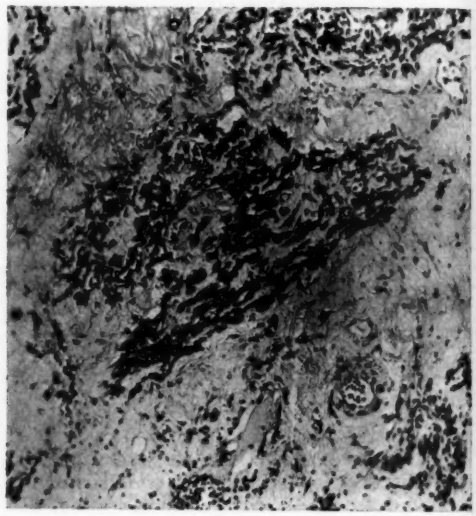

FIGURE III

Atrophy of muscle fibres and fibrosis following radiation (×108)

FIGURE IV

Radiation necrosis. The muscle shows necrosis, atrophy and fibrosis. (×117)

secondary to vascular damage and fibrosis. A recent account of the effects of irradiation on tissues is that of Warren (1943, 1944).

The present series comprises seven lesions of long standing, in some of which irradiation had been applied several years previously. One patient developed necrosis of the muscle seven years after radical mastectomy and radiation treatment.

Histologically the lesions show certain common features. Evident signs of vascular damage are present, many of the blood vessels

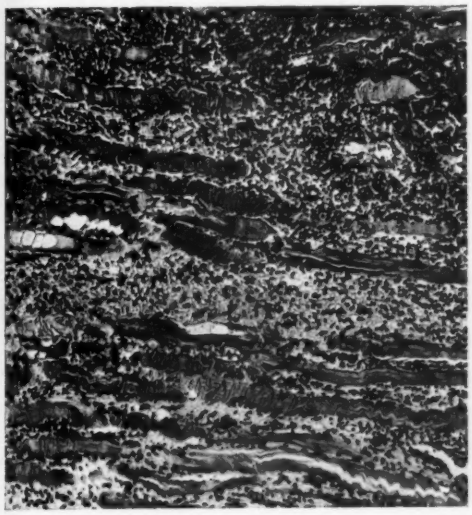

FIGURE V

Chronic inflammation showing separation of the muscle fibres by cellular infiltration. The fibres are undergoing hyaline degeneration and vacuolation. (×108)

being thick-walled and hyaline with partial occlusion of the lumen. In the striped muscle notable changes are found. There are dense fibrosis and separation of the muscle fibres, many of which are greatly atrophied (Figure III). Degenerative changes are often present, the usual finding being a hyaline swelling of the fibre with loss of striation. In two cases the tissue also shows extensive areas of necrosis of muscle (Figure IV) and, in these instances, the large and medium-sized arteries have undergone recent thrombosis.

INFLAMMATION

Simple Inflammation

The present series comprises 16 examples of inflammation in skeletal muscle, in most cases the result of direct extension from neighbouring inflammatory lesions.

Histological examination reveals chronic inflammatory changes in 14 cases. The endomysium and perimysium show focal and diffuse cellular infiltrations, in which many lymphocytes are present with a few plasma cells, and sometimes with polymorphonuclear neutrophile and eosinophile cells intermingled (Figure V). In a few cases the muscle fibres are separated from one another by widespread œdema. The muscle fibres involved in the inflammatory process are in all stages of atrophy and degeneration. Signs of regenerative activity are rarely observed (Figures VI and VII). In the later stages there is fibrosis with breaking up of the muscle, and amongst the fibrous tissue can be seen remnants of atrophic fibres, which appear as small multinucleated masses closely resembling foreign-body giant cells (Figure VIII).

Signs of acute suppurative myositis are evident in two lesions arising from a neighbouring focus of infection. Numerous abscesses

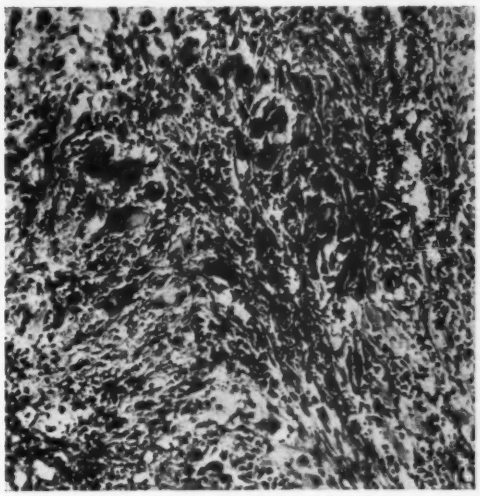

FIGURE VI

Muscle giant cells formed by regeneration in a case of chronic inflammation. (×126)

are formed, and many of the involved muscle fibres are undergoing necrosis with disintegration.

Tuberculosis

Chronic tuberculosis of skeletal muscle is often the result of direct extension from an adjacent lesion. The other recognized mode of infection is by hæmatogenous spread from a distant focus, but this is rarely observed and only a few cases are recorded in the literature (Plummer, Sanes and Smith, 1934). The

relative immunity of skeletal muscle to blood-borne tuberculous infection has been discussed by numerous authors, but without any clear conclusions being reached; it is probable that local chemical factors are concerned. The observed muscle changes arise in two ways. In the first place there is destruction of muscle fibres by the growth of the lesion along the

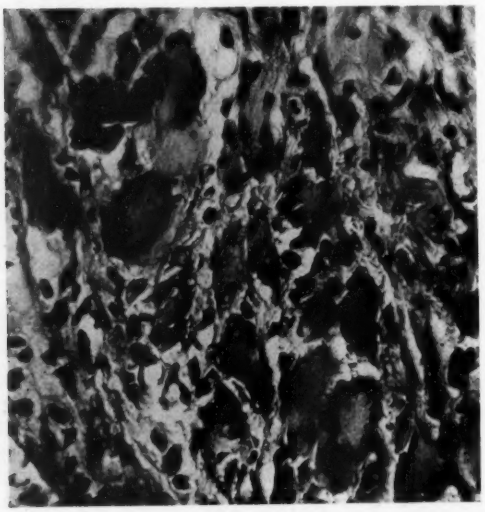

FIGURE VII
High power view of part of Figure VI. (×336)

connective tissue stroma; and secondly, the development of an inflammatory mass results in mechanical compression of the adjacent fibres which then undergo simple atrophy and degeneration.

My own material comprises one tuberculous lesion which has spread into the thoracic muscles from the pleura. Histologically the lesion is composed of abundant granulation tissue with giant-cell systems and small areas of caseation, and in parts there is formation of much fibrous tissue which is spreading into the surrounding muscle. The cellular and fibrous tissue is separating and replacing the striated muscle fibres of the part, and the surviving fibres show the usual changes of atrophy or degeneration.

Syphilis

Tertiary syphilitic lesions of skeletal muscle are rare, and only a few cases are recorded (Levinthal and Miller, 1936; Haines, 1937; Laird, 1938; Kierland and Underwood, 1948). In most of the reported cases gummata, usually single, are present, and these have been described in practically all muscles.

Of six examples studied in the present series, five were localized gummata and one was a diffuse fibrosing myositis. Histologically these lesions show the usual structural changes, including many small thick-walled blood vessels with a considerable degree of periarteritis, and extensive replacement of the muscular tissue by dense fibrous tissue. The residual muscle fibres show degeneration or atrophy; there is very little evidence of regeneration.

Actinomycosis

Actinomycosis of skeletal muscle is uncommon. The mode of infection is usually by direct spread from a neighbouring lesion, but in the later stages there may be spread by the blood-stream.

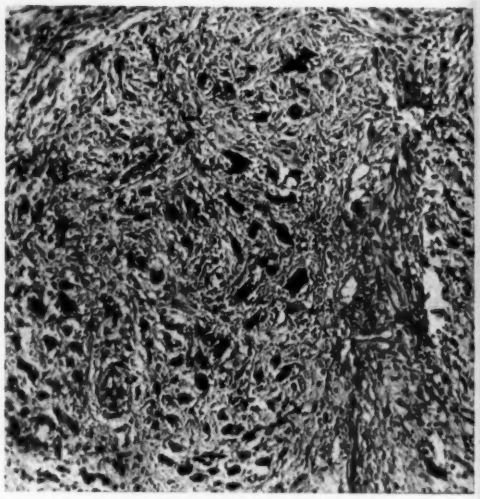

FIGURE VIII
Same case as Figure VI. The multinucleated masses which are atrophic muscle fibres closely resemble foreign-body giant cells. (×130)

One actinomycotic lesion in the muscles of the leg has been studied in the present series. Histological examination reveals an extensive area of suppuration containing colonies of actinomyces and surrounded by a wide zone of inflamed granulation and fibrous tissue. The muscle fibres themselves show notable changes; many have undergone hyaline change or atrophy, and the muscle bundles are widely separated from one another by broad bands of dense connective tissue.

Dermatomyositis

Dermatomyositis is a name applied to a combination of lesions in the skin and muscle. It is a rare disease whose true ætiology has not been determined. The condition has been described by numerous workers, including Keil (1940), Kinney and Maher (1940), and Pagel, Woolf and Asher (1949). The present series included two cases. Microscopic examination reveals degenerative changes in a proportion of the muscle fibres. These are swollen and hyaline, occasionally vacuolated, and a few have undergone necrosis and are being phagocytosed by macrophages. In some areas the muscle fibres are reduced in size and, in places, there is an increase in number of subsarcolemmal nuclei. In certain parts the individual fibres are separated from one another by œdema and

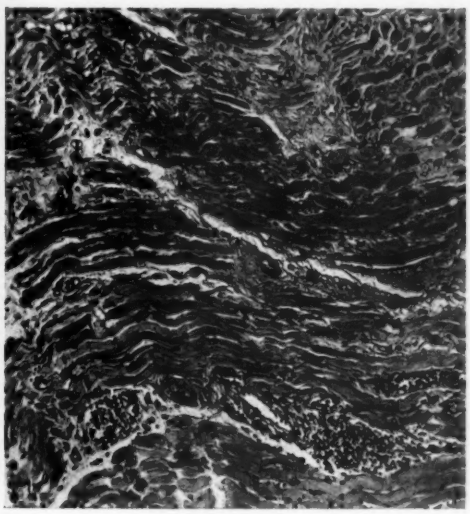

FIGURE IX

Dermatomyositis to show cellular infiltration. (×100)

here and there small foci of chronic inflammatory cells can be seen (Figure IX). The connective tissue between the muscle bundles is œdematous, and in one specimen is increased in amount. The walls of the blood vessels in the connective tissue stroma appear normal, but occasionally the perivascular tissue contains accumulations of inflammatory cells. The observed muscle changes are thus of a non-specific appearance and are similar to those occurring in a wide variety of other lesions.

DEGENERATION

Zenker's Degeneration

Zenker's degeneration is not common. The first report of this type of degeneration was that of Zenker (1864), who studied the muscle changes in many cases of typhoid fever. Since then the muscle changes in this disease, as well as in influenza and other acute infective

FIGURE X

Zenker's degeneration, showing necrosis and fragmentation of the muscle fibres. In other fibres there is proliferation of the subsarcolemmal nuclei. (×90)

processes complicated by bronchopneumonia, have been investigated by numerous workers (Wolbach and Frothingham, 1923; Forbus, 1926).

Two cases are included in the present investigation.

One patient was a woman, aged fifty-two years, who died of bilateral influenzal bronchopneumonia. Portion of the *pectoralis major* muscle was removed for examination. Histologically many of the fibres have undergone a coagulative necrosis and appear swollen and fragmented with loss of their nuclei (Figure X). The fibre may be affected along a considerable part of its length, or it may show one or several necrotic foci of varying size. In some areas the necrotic fibre is invaded by a few polymorphonuclear leucocytes and histiocytes, but often the cellular infiltration is confined to the endomysium and perimysium. In several places the muscle fibres are widely separated by œdema. In other parts there is early fibrosis, and the muscle fibres show either necrosis or atrophy, resulting in much loss of tissue. There are no signs of regeneration.

The second patient was a man, aged seventy-one years, who died three days after the onset of broncho-

pneumonia. The *rectus abdominis* muscle was selected for study. Histologically the muscle shows extensive damage. There is a diffuse and widespread hyaline degeneration of the muscle fibres, which appear swollen with loss of striations, and here and there fibres are also undergoing necrosis and disintegration (Figure XI). There are no infiltrations of inflammatory cells.

These two cases clearly indicate that the essential histological change in Zenker's degeneration is an acute hyaline swelling of the muscle fibres. The inflammatory reaction is inconstant and non-specific, and is related to the damage in the muscle fibre.

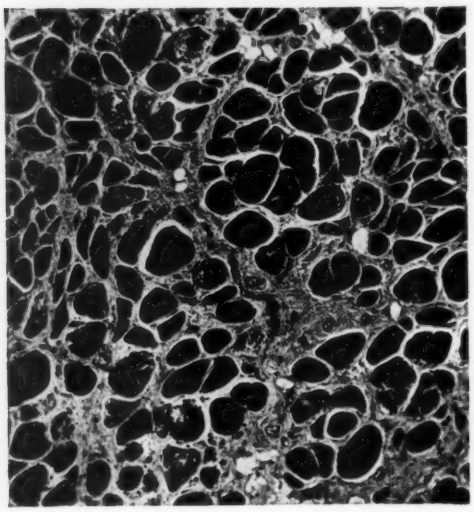

FIGURE XI

Zenker's degeneration. The muscle fibres have undergone widespread hyaline degeneration and necrosis. (×90)

Myasthenia Gravis

The principal finding in the affected muscles in many of the reported cases of *myasthenia gravis* is the presence of small collections of lymphocytes. These cellular foci are often referred to as "lymphorrhages", a term proposed by Buzzard (1905). The muscle fibres often show some pathological change (Keschner and Strauss, 1927; Giordano and Haymond, 1944), but whether this is causally connected with the cellular infiltrations is still regarded by many workers as uncertain. Recently, Russell (1953) has described three types of histological change, one of which produced atrophy of the muscle fibres associated with lymphorrhages, the second coagulation necrosis of the muscle fibres, and the third simple atrophy.

One of the cases in the present series is of interest in that the affected muscle shows widespread degeneration and there is an absence of lymphorrhages. The clinical diagnosis was *myasthenia gravis*, and tissue from the deltoid muscle was submitted for examination. Histologically many of the muscle fibres are undergoing degeneration. The fibres are swollen and hyaline in appearance and on cross-section have an irregular outline. The striations have disappeared and the nuclei are pyknotic. In places the fibres are separated by œdema. The changes in this case thus do not conform to the histological appearances commonly associated with *myasthenia gravis*; they may represent a severe degree of the acute type described by Russell (1953).

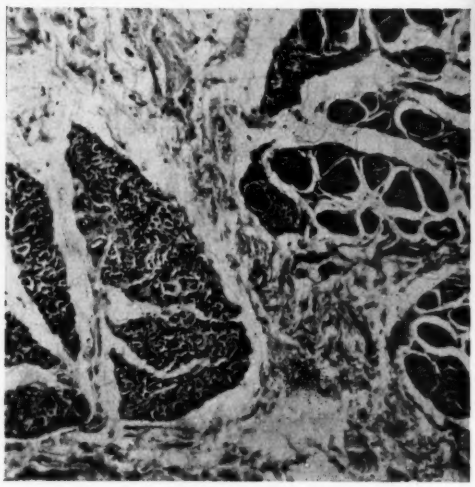

FIGURE XII

Progressive muscular atrophy. Transverse section of muscle to show very atrophic fibres. (×72)

NEUROGENIC ATROPHY

The denervation changes in striated muscle have been studied in man by Bowden and Gutmann (1944), and in animals by many authors including Tower (1935, 1939), Gutmann and Young (1944), and Sunderland and Ray (1950).

My study comprises five cases of neurogenic atrophy. One was a case of progressive muscular atrophy, three were cases of obscure nervous diseases, and the fifth was a case of amyotrophic lateral sclerosis. Histologically the changes in the muscles are distinctive and

follow the same general pattern, except that in disease of the peripheral nerves the atrophic muscle fibres tend to be more uniform in size and less widely dispersed in the muscle bundles than those with spinal cord lesions. Some of the fibres are reduced to fine elements (Figure XII); but the characteristic striated appearance is retained in most instances. The subsarcolemmal nuclei are very numerous, and in places they are arranged in small clusters, especially in the thin fibres. In addition,

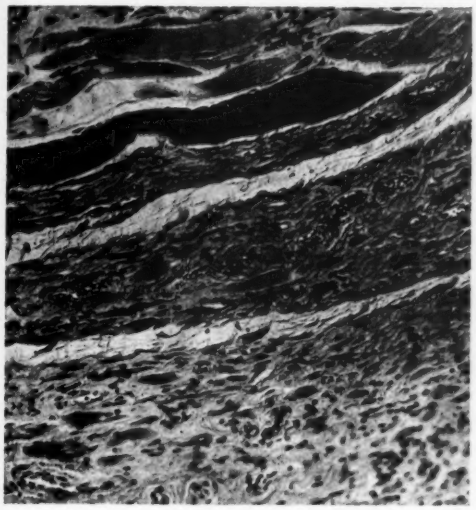

FIGURE XIII

Normal and atrophic muscle fibres in a case of progressive muscular atrophy. The interstitium is increased in amount. (×144)

the atrophic muscle bundles contain a variable proportion of normal fibres; these fibres appear singly or in small groups and they may constitute the bulk of the muscle bundle. They are most numerous with the spinal cord lesions. No degenerative or regenerative changes have been observed in any of the muscle fibres. The interstitial tissue varies in amount; the endomysium and perimysium may show no thickening, but occasionally the individual fibres are separated by a small amount of fibrous tissue (Figure XIII), and the muscle bundles are invested by a thickened perimysium. A small accumulation of adipose tissue has been seen between the muscle fibres and in the thickened perimysium in two of the specimens. The small blood vessels in the connective tissue septa show no abnormalities. The histological changes described are thus substantially similar to those recorded by many authors.

MUSCULAR DYSTROPHY

The terms muscular dystrophy and myopathy are used to designate a group of rare disorders of skeletal muscle whose true ætiology is still debated. No lesions have been observed in the motor neurons or in the nerves, and accordingly, most authors hold the view that the muscular dystrophies are primary diseases of the muscles. A good account of the subject is that of Bramwell (1925), who suggested that the appearances in the muscles might be secondary to changes in the sympathetic nervous system—a suggestion which, however, still remains speculative. Other reports include those of Hurwitz (1936) and Tyler and Wintrobe (1950).

Several varieties of muscular dystrophy have been described, the subdivision being based on the anatomical location of the muscles affected. A type of myopathy in which the lesions occur mainly in the distal parts of the limbs also exists (Welander, 1951). Another form is the pseudo-hypertrophic muscular dystrophy which is associated with a considerable amount of adipose tissue between the muscle fibres. It must be emphasized that in all types of muscular dystrophy the muscles have a common histological structure.

The present investigation includes four examples of muscular dystrophy, three of which were of the pseudo-hypertrophic form in boys aged five, eight and nine years. The other was in a man, aged forty years, who showed marked wasting of the muscles throughout the body.

Except for minor differences, the affected muscles in all four cases show essentially the same morphological changes. Some of the fibres are hypertrophic, others appear relatively normal, whilst a few show varying degrees of atrophy up to complete disappearance. Signs of degeneration are also present, many of the fibres being hyaline in appearance. The changes are sometimes accompanied by an increase in subsarcolemmal nuclei, and in one case of pseudo-hypertrophic dystrophy this was a striking feature and affected the majority of the fibres (Figure XIV). In places a small amount of fibrous tissue is formed between the muscle fibres, and in the pseudo-hypertrophic form there is also an accumulation of adipose tissue in the endomysium and perimysium. No obvious changes have been observed in the blood vessels and nerves of the affected muscles.

VASCULAR DISEASE

Polyarteritis Nodosa

The ætiology of *polyarteritis nodosa* is unknown, but evidence of an indirect nature suggests that it is a manifestation of hypersensitivity (Rich, 1942, 1946–47). The lesions are widespread in many organs, and the skeletal muscles are affected in a large proportion of cases. According to Arkin (1930) the muscles are implicated in 30% of cases, but the results of biopsy suggest a much higher incidence. The condition has also been described in a number of animals, the changes recorded being comparable histologically with those seen in the human subject.

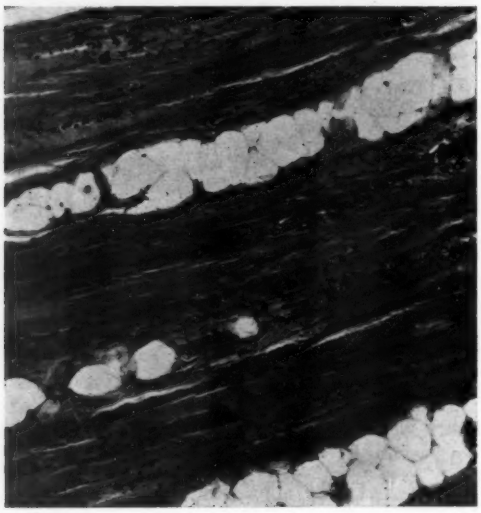

FIGURE XIV

Pseudo-hypertrophic muscular dystrophy, to show proliferation of the subsarcolemmal nuclei and the adipose replacement. (×99).

The present study included two cases of *polyarteritis nodosa* in the human subject, and similar lesions in two animals, an ox and a rat. Microscopically the arterial lesions form a striking feature ranging from necrosis and acute inflammation of the vessel wall to granulation tissue formation. Large numbers of eosinophile leucocytes are usual in the cellular infiltration. Occlusion of the vessels by thrombosis is a frequent occurrence, and in places there is a suggestion of early aneurysmal dilatation. All these changes are present in varying degree, but sometimes the histological picture is uniform, many of the lesions being in the same stage. In some cases there is evidence of old hæmorrhage in the perivascular tissue in the form of small collections of deeply staining blood pigment. Some of the muscle fibres have undergone hyaline degeneration or vacuolation; others show atrophy and appear as small scattered foci in the muscle bundles, the changes resembling those seen in neurogenic atrophy. Mild perivascular and diffuse infiltrations of chronic inflammatory cells are also occasionally observed in the endomysium and perimysium.

"Giant-cell" or "Temporal" Chronic Arteritis

"Giant-cell" or "temporal" chronic arteritis is a rare disease of unknown ætiology, characterized by subacute inflammation of the media and adventitia, foci of necrosis in the media, and the formation of foreign-body giant cells. The small arteries are frequently occluded by thrombosis, and the tissues supplied by these vessels may suffer the effects of ischæmia. The vascular lesions are not limited to the temporal arteries, but occur also in the aorta and in many other arteries. Useful accounts of this disease include those of Gilmour (1941) and Gartside (1944).

The present series includes two cases of "temporal" arteritis in which the affected artery in each instance is almost completely occluded by an organizing thrombus. Histologically there are no significant structural changes in the muscle in the immediate vicinity of the affected vessel. In one case the cellular infiltration in the vessel wall extends into the perivascular connective tissue and between a few of the adjacent muscle fibres; in the other case the muscle fibres have undergone a mild degree of atrophy.

Vascular Occlusion

The rich anastomotic blood supply of the skeletal muscle renders this tissue relatively insusceptible to the effects of arterial obstruction. However, if vascular occlusion is extensive or involves a main artery, especially if the vessel wall is the seat of disease, an adequate collateral circulation may not be available and necrosis of the tissue will result. The histological changes of skeletal muscle following vascular injury in man have been studied recently by Bowden and Gutmann (1949). The following examples of vascular occlusion in skeletal muscle have been observed.

Arterial Thrombosis; Thrombosis of a Main Artery of the Lower Limb.—The affected muscle in one case has been studied. Histologically there is widespread necrosis of the muscle

deprived of its blood supply. The muscle fibres are swollen, hyaline, and devoid of nuclei and striations. Many are invaded and replaced by histiocytes and other inflammatory cells, and in places there is diffuse infiltration of the necrotic tissue by large numbers of polymorphonuclear leucocytes. Fibroblasts also contribute to the cellular content, and often they are seen to form an investing sheath around each damaged fibre.

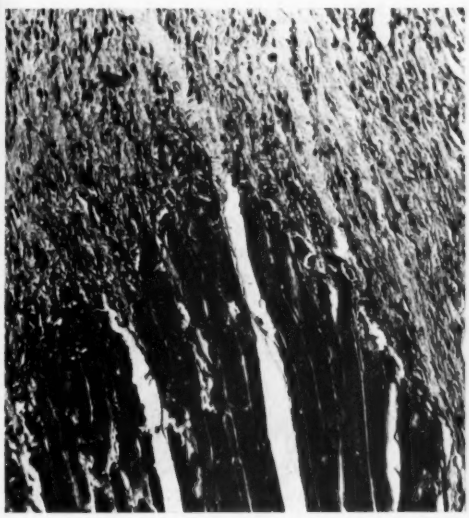

FIGURE XV

Volkmann's ischæmic contracture. The necrotic muscle is surrounded by fibrous tissue. (×120)

Volkmann's Ischæmic Contracture

Volkmann's ischæmic contracture is a rare condition. It develops as the result of injury to the muscles, often follows a fracture, and occurs most frequently in the region of the elbow. There is no agreement as to the mode of production. According to Brooks (1922), Middleton (1930) and others, venous obstruction appears to be the essential factor, leading to hæmorrhage into the muscle. The muscle undergoes necrosis, and this is followed by fibrosis with resulting contraction. This theory is disputed by Griffiths (1940), who considers that the contracture is the result of arterial occlusion.

One case of Volkmann's contracture in a man, aged twenty years, has been studied. Microscopically there is massive necrosis of the muscle fibres with preservation of the cross striations. A wide zone of dense connective tissue, containing scattered small collections of pigmented phagocytes, surrounds the necrotic muscle. In addition a cellular infiltration of histiocytes and fibroblasts is present at the margin of the damaged muscle, between it and the fibrous tissue zone (Figure XV).

Ischæmic Fibrosis

The following case is of interest in that it shows changes which represent the late phase of injury to muscle.

The patient was a boy, aged fifteen years, who gave a history of injury to the soft tissues of the thigh. Several months later a firm swelling appeared in the sartorious muscle of the injured side. The whole muscle was excised at operation, and a portion of densely fibrotic muscle was received for examination. Histologically the muscle tissue is partly replaced by dense connective tissue, and many of the surviving muscle fibres show varying degrees of degeneration (Figure XVI). Some are hyaline, circular in outline and greatly increased in size, measuring up to 92μ in diameter as compared with a mean diameter of 36μ of the normal fibres present in the periphery of the muscle. Occasionally the subsarcolemmal nuclei lie in the depth of the fibre. Atrophic fibres and others showing vacuolation are also numerous. Small scattered foci of chronic inflammatory cells are common.

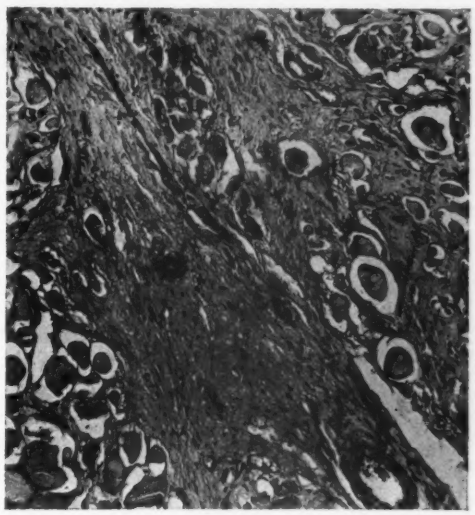

FIGURE XVI

Ischæmic fibrosis. The muscle fibres show hyaline degeneration and vacuolation. (×108)

The ætiology of this lesion is probably similar to that of Volkmann's ischæmic contracture and of congenital torticollis. Of particular interest in this regard are the experimental findings of Middleton (1930), who produced similar changes in the sartorius muscle by venous occlusion.

Secondary Tumours

Direct invasion of the skeletal muscle by neighbouring growths is common. On the other hand, blood-borne metastases are rare; in a series of 500 consecutive cancer necropsies Willis (1952) saw metastases in skeletal muscle in only four cases.

My series comprises 34 secondary tumours, most of which are carcinomata. Eleven of the tumours are metastases from distant carcinomata, and the remainder are direct extensions from tumours arising in neighbouring tissues. The types of tumour and their relative frequencies are given in Table I. Many of the less usual tumours were referred for consultative opinion, and therefore the figures do not represent a true census. The method of spread in the muscle is by infiltration along the perimysial connective tissue and between the fibres; four of the metastatic tumours also show evidence of intracellular invasion of some of the muscle fibres, which are seen to contain groups of carcinoma cells in their sarcoplasm.

TABLE I

Type of Tumour	Metastases	Direct Extension from an Adjacent Tumour
Carcinoma	11	16
Malignant melanoma	—	1
Osteogenic sarcoma	—	1
Malignant synovioma	—	1
Solitary plasmocytoma of bone..	—	2
Chloroma	—	1
Chordoma	—	1

The changes in the muscle are those of atrophy and degeneration, and seldom are there signs of regeneration. Many of the invaded muscle fibres show varying degrees of atrophy, and frequently these structurally altered fibres contain small aggregates of deeply-staining subsarcolemmal nuclei. Degenerative changes are also present in these surviving fibres. The most common change is a hyaline degeneration, and very occasionally a swollen hyaline fibre shows a spreading of its sub-sarcolemmal nuclei into the interior of the cell. Vacuolation of the fibres is sometimes observed. The connective tissue is increased in amount and often contains collections of chronic inflammatory cells.

A few of the tumours have produced pressure effects in the zone of muscle fibres immediately beyond the tumour margin. In this region the muscle fibres are atrophic, such a change usually being accompanied by an overgrowth of interstitial connective tissue. Some of the fibres also show degenerative changes. Small foci of chronic inflammatory cells are sometimes present in the fibrous tissue. Regressive changes are less in evidence a short distance beyond the tumour margin, and only a few scattered fibres reveal atrophy or degeneration. Occasionally a muscle fibre of normal size contains numerous subsarcolemmal nuclei which are arranged uniformly throughout the sarcoplasm.

In only one lesion are there signs of muscle regeneration. In this instance a few muscle fibres have formed bulbous multinucleated masses strongly suggestive of regenerative activity.

MISCELLANEOUS LESIONS

Trichinosis

Trichinosis is the most common of the parasitic infections of muscle. The parasites have an affinity for the striated muscle fibres, but the reason for this is not known.

One case of trichinosis has been examined. The parasites have penetrated the muscle fibres and are ensheathed by a thick capsule of hyaline connective tissue. No significant changes can be seen in the adjacent tissues and there is no evidence of an inflammatory reaction.

Endometriosis

My study included one case of endometriosis of the abdominal wall which followed an operation for ventral fixation of the uterus. Histological examination revealed typical endometrial tissue embedded in dense fibrous tissue. The skeletal muscle was involved by the scar tissue and in places showed great atrophy.

LESIONS IN THE TONGUE

The muscle changes were studied in 63 lesions of the tongue, including 27 inflammatory lesions, 18 squamous-cell carcinomata involving the muscle, and eight irradiated carcinomata. Of the remainder, amyloidosis was present in one and a keloid in another.

Histologically most of the lesions show structural changes in some muscle fibres. The changes are usually those of degeneration and atrophy, and occasionally both of these features are present together in the one lesion, particularly in the carcinoma group. Often the muscle changes are mild, but they may be severe and widely distributed. The most extreme degree of atrophy has been found in several of the irradiation cases, the fibres being reduced to very thin elements, with rows or clumps of nuclei centrally placed which lie in a stroma of dense fibrous tissue. The muscle fibres implicated in keloid show also somewhat

similar appearances. Signs of degenerative changes are common and are most frequent in the various inflammatory states. The fibres are swollen, sometimes hyaline in appearance, and stain weakly with eosin, and some have lost their cross striations. In a few instances the fibres are vacuolated and the nucleus is pyknotic or swollen. Actual necrosis of the muscle fibres has been observed in one of the irradiation cases.

Regeneration of the muscle fibres has been noticed in one inflammatory lesion. The change is limited to several fibres which show small multinucleated plasmodial outgrowths. In one other case, also an inflammatory process, there are a few widely dispersed fibres which stain weakly with eosin and reveal nuclear proliferation. Such an appearance seems to have resulted from the recovery of previously damaged fibres.

CONCLUSIONS

Frequent findings in skeletal muscle involved by disease include those of degeneration and atrophy, and often both these features are present together in varying degree in the one lesion. Signs of regenerative activity are rarely observed in the damaged muscle.

Degeneration usually manifests itself as a hyaline swelling, and this structural change is sometimes associated with necrosis of the muscle fibre. Inflammatory changes develop secondarily in the supporting connective tissue, and the necrotic fibre is invaded and phagocytosed by histiocytes and other inflammatory cells.

The main change in neurogenic lesions and in ischæmia produced by vascular disease is atrophy of the fibre, and a similar result is induced by mechanical compression.

Multinucleated giant cells of muscle origin are sometimes observed, especially in muscular tissue involved in a fibrotic process. They are usually present in large numbers in muscle regeneration produced experimentally. These muscle giant cells may be almost indistinguishable from foreign-body giant cells, and careful study, together with special stains, will then be necessary for their recognition.

All these changes in the muscle fibre are of a non-specific character, and seldom can they be regarded as distinctive of any particular pathological process.

The diagnosis of a muscle lesion must therefore be based not only on the structural changes in the fibre, but also on the findings in the supporting connective tissue of the muscle and on the clinical and pathological features in other structures. However, it must be emphasized that the changes in the interstitial connective tissue of the muscle are not necessarily of a specific nature; they may be secondary to damage of the fibres.

ACKNOWLEDGEMENTS

I am most grateful to Professor R. A. Willis for his interest in this work, and to Professor M. J. Stewart for material from his files. My thanks are due to Mr. W. H. Lawson for the photomicrographs. I am indebted to the Chairman of the Repatriation Commission for permission to publish this paper.

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NEONATAL NEPHRITIS[1]

L. I. TAFT[2]

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IN the past, small scarred kidneys found at necropsy in neonates have been referred to commonly as "hypoplastic" or "atrophic"; but it is now recognized that many of them show the changes of inflammation. While these changes usually resemble those of pyelonephritis, a number of cases has been reported in which the histological changes resemble those of glomerulonephritis (Mitchell, 1930).

Nevertheless Potter (1952), in her text-book "Pathology of the Fetus and the Newborn", makes the following statement:

> Glomerulonephritis is unknown in the newborn. Rarely a few partially hyalinized glomeruli can be found in the parenchyma of otherwise normal kidneys. They result from a malformation of the glomerular tuft and are unrelated to an infectious process.

The purpose of this paper is to examine such statements and their implications.

A survey of 1200 necropsies, performed at the Royal Children's Hospital, Melbourne, over a six-year period from 1949 to 1954, was made in order to determine the incidence and nature of neonatal glomerulonephritis. The histories and pathological findings in two cases in which the diagnosis of neonatal glomerulonephritis could reasonably be entertained are herewith presented and discussed. By contrast, in the same period pyelonephritis associated with urinary tract anomalies and/or septicæmia was found in 49 babies that had died within the first year of life.

CASE I.—R.M., a male baby, was born at term after a normal pregnancy and labour. Intermittent diarrhœa commenced at the age of five days, and when he was three weeks old he was admitted to the Royal Children's Hospital, Melbourne, in a state of moderate dehydration. Fluids were given via a gastric tube, but two days later he had developed pitting œdema of the feet, legs and eyelids. Twitching of the face and limbs also occurred. Albuminuria and microscopically evident hæmaturia were detected. Both recurred frequently throughout the course of his illness. Epithelial cells, and hyaline, granular and cellular casts were frequently present in the urine. Pus cells were seen in the urine on one occasion when only 0 to 1 pus cell per high-power field was found in the centrifuged deposit. The urine was examined by culture on two occasions. A scanty growth of *Staphylococcus aureus* and *Staph. albus* was once obtained from a non-catheter specimen, no organism being grown from the other specimen. Attempts at culture of microorganisms from the stools were persistently unsuccessful. The biochemical findings in the blood and serum throughout the course of the baby's illness are presented in Table I. Apart from a slight increase in protein content, the cerebro-spinal fluid was normal. Correction of the electrolyte disturbance was attempted by the intramuscular administration of calcium gluconate, while calcium lactate and sodium lactate were given orally. Fat necrosis subsequently developed

[1] Received on October 10, 1955.

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TABLE I

Case I: Clinical and Biochemical Findings

	Days after Admission to Hospital								
	2[1]	3[2]	10[3]	30	36[4]	39	46	52[5]	58
Serum sodium (milliequivalents per litre)	—	104·0	126·0	—	122·0	127·0	137·0	124·0	127·0
Serum potassium (milliequivalents per litre)	—	4·7	6·1	—	5·8	6·4	6·2	—	6·5[6]
Serum calcium (milliequivalents per litre)	3·25	5·3	5·3	—	4·2	3·0	3·5	4·0	4·8
Serum chloride (milliequivalents per litre)	—	77·0	89·0	—	108·0	103·0	108·0	99·0	103·0
Serum phosphate (milliequivalents per litre)	4·0	5·8	3·9	—	5·3	5·8	5·8	—	5·4
Serum sulphate (milliequivalents per litre)	—	—	—	—	—	—	10·0	—	—
Alkali reserve (milliequivalents per litre)	—	12·0	17·8	—	9·0	11·0	16·0	—	—
Serum proteins (grammes per 100 millilitres)	3·8	3·4	4·4	—	4·6	4·6	4·6	5·4	—
Blood urea (milligrammes per 100 millilitres)	—	56·0	—	77·0	36·0	—	146·0	—	120·0

[1] Œdema and twitching noted; intramuscular administration of calcium gluconate commenced.
[2] Albuminuria first noted; oral administration of calcium lactate commenced.
[3] No œdema.
[4] Vomiting, diarrhœa; sodium lactate given orally.
[5] Vomiting attacks and œdema becoming persistent.
[6] Some hæmolysis in serum specimen.

in the subcutanea of the thighs and buttocks at the site of the calcium gluconate injections. Progressive anæmia necessitated blood transfusions on two occasions. Seborrhœic dermatitis of the scalp and flexures responded to local treatment. Vomiting, diarrhœa, dehydration and acidosis recurred, and œdema of the eyelids and legs became persistent.

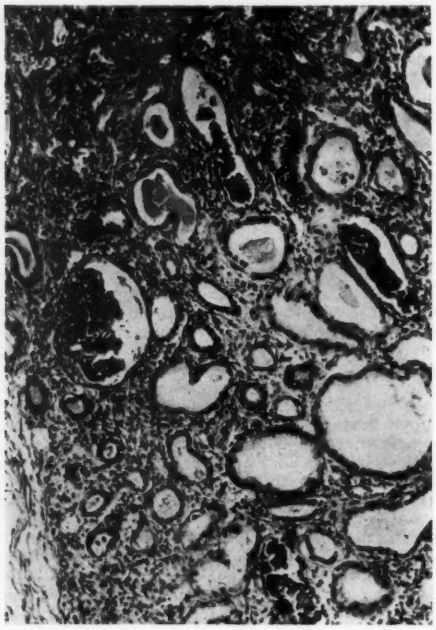

FIGURE I

Case I Photomicrograph of a section of kidney in neonatal nephritis. Digitation of tufts, loss of capillary lumina and intracapsular exudate are present in the glomeruli. The dilated tubules contain casts. There is increased interstitial tissue with many small round cells. (×90)

The infant failed to thrive and died sixty-seven days after his admission to hospital.

At necropsy it was found that both kidneys were small, the right weighing 1·5 grammes, the left 4·0 grammes (the normal neonatal kidney weighs approximately 13 grammes). The capsules stripped to leave a slightly granular surface. Small cystic structures were visible under the capsule of the left kidney. Corticomedullary demarcation was poor, and the renal pyramids were deformed, with absence of medullary rays. The renal pelves, the ureters, the bladder and the urethra were normal. Both renal arteries were small. There was no cardiac enlargement, but terminal broncho-pneumonia was present. The subcutaneous lumps in the thighs and buttocks were found to consist of islands of calcified necrosed fat surrounded by granulation tissue containing foreign-body giant cells.

Microscopic examination of the kidney confirmed the macroscopically evident structural disorganization (Figures I, II and III). The glomeruli were grossly reduced in numbers, those present showing enlargement, increased cellularity and some digitation of the tufts with occlusion of the glomerular capillaries. Intracapsular exudate, red cells and adhesions could be seen. Other glomeruli showed progressive degrees of fibrosis and hyalinization. Epithelial crescents were not seen. Islands of grossly dilated tubules, lined by hypertrophic epithelium, were present, particularly under the capsule of the left kidney, where macroscopically they had presented the appearance of cysts. Other tubules were lined by flattened cells, while some tubules were dilated and others were small. Hyaline and granular casts were visible in the lumina of the tubules. The collecting tubules were generally normal. Some primitive nephrogenic tubules were visible under the capsule. The stroma was greatly increased in amount, containing fibroblasts, small round cells and histiocytes as well as numerous capillaries. There was thickening of both the media and the intima of the smaller renal arteries and the arterioles.

FIGURE II

Case I. Photomicrograph showing increased cellularity, obliteration of capillary lumina, capsular adhesions and fibrosis in the glomeruli. Casts are present in adjacent collecting tubules. (×180)

CASE II.—M.K., a female baby, aspirated thick mucus into her lungs at birth and was cyanosed for several days. She had a persistent non-productive cough. When aged three weeks, she began vomiting her feeds. She was admitted to the Royal Children's Hospital, Melbourne, when four weeks old. Her weight had fallen from six pounds three ounces at birth to five pounds twelve ounces. Other than her poor nutrition there were no positive findings on physical examination. Radiological examination of the chest revealed no abnormality. Red cells in the

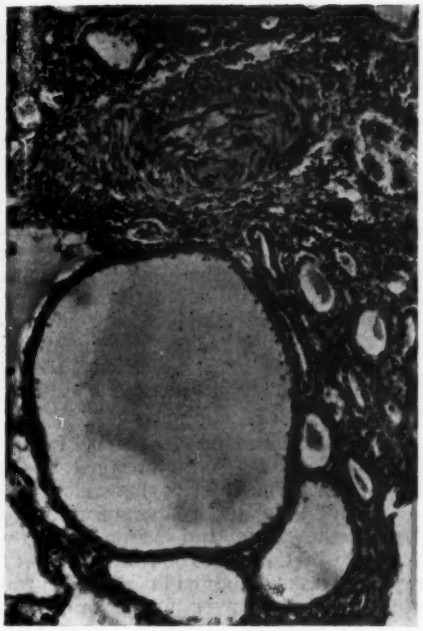

FIGURE III

Case I. Grossly dilated tubules and thickening of walls of small renal artery. (×180)

FIGURE V

A group of glomeruli showing tuft digitation and loss of capillary lumina. Dilated tubules contain casts. Primitive nephrogenic tubules are visible in the thickened renal capsule. (×90)

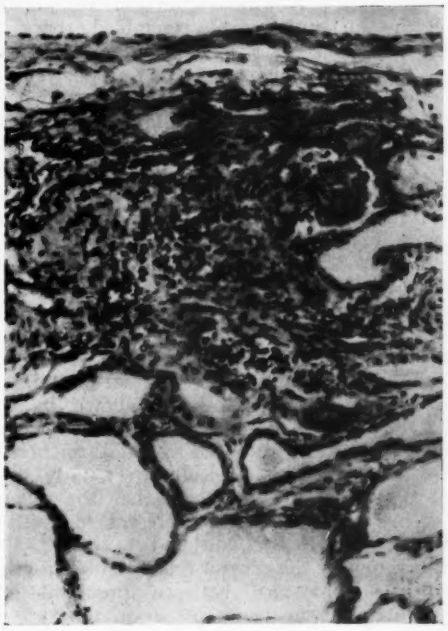

FIGURE IV

Case II. Photomicrograph of section of kidney showing tuft digitation in glomerulus, dilated tubules, and increased fibrous tissue infiltrated with small round cells. (×135)

FIGURE VI

Nodules of cartilage are present in the interstitial tissue. Dilated tubules contain casts. There is thickening of the wall of a small renal artery. (×90)

cerebro-spinal fluid were due to a traumatic lumbar puncture. Cultures from the stools showed no significant pathogens. There was little improvement in her condition despite feeding adjustments, sedation and gavage feeds. Death occurred suddenly two weeks after her admission to hospital.

At necropsy both kidneys were considerably reduced in size and were friable in consistency. Examination of cut sections revealed loss of normal renal architecture with poor cortico-medullary demarcation and numerous cystic spaces throughout the renal substance. The ureters, bladder and urethra were normal. Abnormalities of the renal arteries were not noted. There was no cardio-vascular abnormality, but hypostatic pulmonary congestion was present.

Microscopic examination of the kidney revealed disorganization of structure (Figures IV, V and VI). The glomeruli were greatly reduced in number, those present showing increased cellularity and digitation of the tufts, and periglomerular and intraglomerular fibrosis progressing to hyalinization. The tubules were grossly dilated, resembling cysts, but were lined by hypertrophic or atrophic epithelial cells. They contained casts which were mainly hyaline in type. The stroma was increased in amount, consisting of cellular fibroblastic tissue with some small round cells and nodules of cartilage. There was some thickening of the media of the renal arterioles. Nephrogenic tubules were in evidence under the capsule.

DISCUSSION

Necropsy in each case revealed shrunken kidneys with structural deformity, cystic changes and scarring. The histological appearance resembled that of glomerulonephritis, showing parenchymal damage, cellular infiltration, proliferative phenomena and fibrosis. Increased cellularity of the tufts, capsular exudate and adhesions were seen in the glomeruli, with red cells and casts in the tubules. Tuft digitation and capillary obliteration had progressed to hyalinization of many glomeruli. Islands of dilated subcapsular tubules were lined by hypertrophic or flattened cells, while other tubules were shrunken and lined by irregular atrophic epithelium. The number of nephrogenic tubules seen indicates that increased nephrogenesis continued after term, probably under the stimulus of renal failure. The nodules of cartilage seen in the kidney in Case II probably represent post-inflammatory metaplasia. In Case I the kidneys presented the appearance of active inflammation with gross fibroblastic proliferation. In Case II there was considerably less activity; but in both cases the degree of change in the kidneys, taken in conjunction with the duration of life, suggests onset of the disease *in utero*.

Collins (1954) has recorded glomerulonephritis in a new-born baby who he considered had developed the disease *in utero*. Thompson (1951) reported the occurrence of an upper respiratory tract infection during the second trimester of pregnancy in a woman who subsequently gave birth to a baby who died of glomerulonephritis in the neonatal period. Thompson suggested that the disease developed in the fœtus in a manner similar to that occurring in older children. The pathological findings recorded by both these authors resemble those of Case I.

Friedman *et alii* (1942) demonstrated endothelial hyperplasia obliterating glomerular capillaries in a number of neonatal kidneys. This change was associated with capsular proliferation progressing to hyalinization of the glomeruli. In most of their cases only a few glomeruli were affected, but in some of them more diffuse involvement produced the clinical and pathological changes characteristic of glomerulo-nephritis.

The clinical manifestations of renal failure in infancy are usually gastro-intestinal in type, and ante-mortem diagnosis of glomerulonephritis is made on the results of laboratory investigations of the urine and serum. This was exemplified by Case I. The renal origin of the symptoms was unsuspected in Case II, in which these investigations were not performed.

That other types of renal damage can occur *in utero* is illustrated by the finding of small scarred kidneys in neonates with urethral obstruction by valves, chronic pyelonephritis and congenital syphilis. Potter (1952) described a group of polycystic kidneys in neonates in which the appearances resembled those in Case II. The cystic changes in these kidneys are the result of inflammation and obstruction in and around the tubules, and not due to genetic factors. There is no familial incidence, nor are cystic changes detected in other organs such as the liver, lung and pancreas in these cases.

It is probable that the variations in pathological appearances encountered depend on the nature of the damaging agent and its effects on the fœtal kidneys at different stages of their development, just as, in the adult, chronic nephritis may result from different causes and present certain differences in histological findings. The gross degree of structural and connective tissue change, as shown by the contraction and granularity of the kidney seen macroscopically, and the amount of fibrous tissue observed histologically at an early stage of post-natal life, indicates that the inflammatory process has been present for such a period that it was initiated *in utero*; this thus supports the general thesis that there is no essential difference between pre-natal and post-natal tissue reactions, or in the type of factors causing them.

SUMMARY

Glomerulonephritis occurs in the neonatal period, but is a rare finding at necropsy. Two cases (one male subject and one female) were found in 1200 necropsies performed between 1949 and 1954 at the Royal Children's Hospital, Melbourne.

The histories and pathological findings in these two cases are presented and discussed.

Laboratory investigation of urine and serum is necessary to diagnose the disease *ante mortem*.

These and other cases reported in the literature suggest that the disease process is initiated *in utero*, and that the pathogenesis is comparable to that observed in glomerulonephritis in later life, modified by the developmental processes taking place in the kidney at that time.

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THE RELATIONSHIP BETWEEN DOSAGE AND UTILIZATION OF ORALLY ADMINISTERED IRON COMPOUNDS[1]

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THE range of therapeutic dosage of iron compounds varies within wide limits. Some clinicians believe that large doses are necessary to obtain maximum benefit, whereas others contend that satisfactory results follow administration of small amounts. The latter hold that increased dosage is not followed proportionately by increased absorption and is more likely to produce gastro-intestinal irritation. Hahn *et alii* (1940) investigated the problem in dogs rendered anæmic by repeated removal of blood. They administered various ferric iron compounds tagged with radioactive iron and later assayed the blood for radioactivity. It was found that as the dose of iron was increased the percentage appearing in the blood decreased.

The experiments reported in this paper were undertaken to investigate the relationship between dosage and absorption in non-anæmic rats. Varying quantities of iron containing a constant amount of radioactive iron were fed to normal rats in single doses. After twenty-one days the radioactivity of the blood, liver and spleen indicated the amount of the administered iron which had been absorbed by the animals. A significant percentage of the absorbed iron was found in the liver and spleen. Hahn *et alii* (1940) ignored the radioactive iron in these organs and because their animals were iron-deficient this did not affect the validity of their results. In the iron-deficient animal the stores in the liver and spleen are virtually depleted.

It is generally believed, following the work of Lintzel (1933), that iron must be in the ferrous or reduced form before it can be absorbed. If this is correct, ferric iron must be reduced before it becomes available. In the present work both ferric and ferrous compounds were investigated.

[1] Received for publication on March 6, 1956.

METHODS AND MATERIALS

Experimental Animals

Male albino rats weighing between 267 and 407 grammes were used. They were fed on a diet of compressed pellets obtained from the Animal Health Products Proprietary Limited, Sydney.

Radioactive Iron

Two batches of Fe^{59} were obtained from the Atomic Energy Research Establishment, Harwell, through the agency of the Commonwealth X-Ray and Radium Laboratory, Department of Health. The first consignment of five millilitres contained 0·765 milligramme of Fe^{59}, the activity being 98·7 microcuries. The Fe^{59} was in the form of ferric chloride. The solution was diluted to 31 millilitres with distilled water, after which the iron concentration was 0·025 milligramme per millilitre. The second consignment of two millilitres was also in the form of ferric chloride, and contained 1·14 milligrammes of Fe^{59} with an activity of 150 microcuries on date of arrival. The iron in this solution was converted to the ferrous form. The stock solution of two millilitres was diluted to 33 millilitres with distilled water and 0·5 millilitre of concentrated sulphuric acid was added. Ferrous sulphide (FeS) was precipitated by adding two millilitres of ammonium sulphide solution (Analar B.D.H.) dropwise. The precipitate was filtered on to a Whatman 44 paper and immediately dissolved from the paper with $N/2.H_2SO_4$. The resulting solution was again passed through the paper and the paper was washed with additional $N/2.H_2SO_4$ until the volume of the filtrate was 6·6 millilitres. The iron was now in the form of ferrous sulphate. A previous experiment in which non-radioactive iron was reduced by this method showed that there was 100% reduction, with no loss of total iron. The ferrous sulphate solution was diluted to 33

millilitres with distilled water immediately before use, so that the concentration of iron was then 0·069 milligramme per millilitre in $N/10.H_2SO_4$.

Administration of Iron

Experiment I. Experiment I was performed with ferric iron. The Fe^{59} solution was divided into five equal parts of six millilitres. To four of these aliquots varying amounts of ferric chloride were added so that the total iron of the five samples was 0·025, 1·025, 3·025, 5·025 and 10·025 milligrammes per millilitre. Under light ether anæsthesia a thin polythene tube was passed through the mouths into the stomachs of the rats and one millilitre of each solution was administered to each of six rats in the five groups. Immediately after injection of the iron solution, a further three millilitres of distilled water were passed through the tubing.

Experiment II. In experiment II the iron was administered as ferrous sulphate. The Fe^{59} solution was divided into six equal parts of 5·3 millilitres. To five of these aliquots varying amounts of ferrous sulphate were added, so that the total iron of the six samples was 0·069, 0·569, 1·069, 3·069, 5·069 and 10·069 milligrammes per millilitre. As in experiment I, one millilitre of each solution was administered to each of five rats in the six groups, except that in this case only 2·0 millilitres of distilled water was used for washing the tube.

Collecting Specimens

Three weeks after the iron was administered the animals were sacrificed. Under light ether anæsthesia, the abdominal cavity and the chest were opened in the mid-line and blood was collected from the heart with a needle and syringe containing heparin. Approximately 10 millilitres of blood were obtained from each animal, the actual volume being noted. Viviperfusion was then performed to remove blood contained in the liver and spleen. Physiological saline was introduced into the inferior *vena cava* and the perfusate was allowed to escape from the incised carotid vessels. During the perfusion, which was continued until the perfusate contained only minimal amounts of blood, the liver became pale. The liver and spleen were excised and weighed.

Radioassay of Samples

The blood, liver and spleen from each animal were digested with sulphuric and perchloric acids and the radioactivity measured as previously described (Walsh *et alii*, 1955).

In both experiments aliquots of the isotopic solution as administered to the rats was appropriately diluted for radioassay. The radioactivity of the administered doses was then calculated.

Calculation of Results

The total absorbed iron present in the circulation of each rat was calculated from the radioassay results of the aliquot of blood taken and the total blood volume of the animal. For these purposes the blood volume of the rat was taken to be 67 millilitres per kilogram of body weight. An example of the calculation follows.

Rat No. 4: Series I of experiment with ferrous sulphate

Weight	.. .. ..	311 grammes
Volume of blood taken	..	9 millilitres
Counts per minute (c.p.m.)		623

Total blood volume .. $\frac{311}{1000} \times 67$ ml.

Total radioactivity in circulating blood $\frac{311}{1000} \times 67 \times \frac{623}{9}$ c.p.m.

$= 1442$ c.p.m.

From this value and the counts per minute (c.p.m.) of the iron solution administered (7950 c.p.m.) the percentage of the administered iron which was absorbed and appeared in the blood was calculated: $\frac{1442}{7950} \times 100 = 18{\cdot}1\%$. The absolute amount of iron absorbed from the dose is calculated from the total amount administered and the percentage appearing in the body, that is, in the blood, liver and spleen. It is probable that a small amount of the absorbed iron is located in other parts of the body, such as the bone marrow, but this has been ignored in the present work.

In all these experiments it is, of course, assumed that there is complete mixing of radioactive with non-radioactive iron and that the animal will absorb either without discrimination.

RESULTS

The results of the first experiment in which ferric iron was given are shown in Table I. The amount of iron absorbed increased progressively as the dose was increased, so that approximately 30 times as much was absorbed from a dose of 5·025 milligrammes as from a dose of 0·025 milligramme. However, the percentage absorption decreased from 38·8% with a dose of 0·025 milligramme to 6·4% with a dose of 5·025 milligrammes. In general,

TABLE I

The Utilization of Ferric Iron Administered Orally to Rats

Observation	Series				
	I	II	III	IV	V
Amount of iron administered (milligrammes)	0·025	1·025	3·025	5·025	10·025
Number of rats	5	4	5	4	5
Mean weight (grammes)	347·0	313·0	334·0	355·0	343·0
Total iron absorbed from dose: mean ± standard error[1] (milligrammes)	0·010±0·004	0·077±0·021	0·182±0·042	0·320±0·018	0·491±0·093
Percentage of iron absorbed (mean)	38·8	7·5	6·0	6·4	4·9
Percentage of absorbed iron in blood (mean)	90·2	88·9	91·7	91·9	82·2
Percentage of absorbed iron in liver (mean)	8·5	11·1	8·3	8·1	17·8
Percentage of absorbed iron in spleen (mean)	1·3	0	0	0	0

[1] Standard error of the mean is obtained from $\frac{\sigma}{\sqrt{n-1}}$ where n is the number of observations.

similar findings were obtained in the second experiment in which ferrous iron was administered (Table II). It should be noted that the smallest dose used in Series I of the second experiment was higher than the corresponding dose in the first experiment. This explains the smaller percentage absorption in Series I of the second experiment. It was also found that the percentage absorption and the absolute amount absorbed from ferric iron was greater than from ferrous iron at all dosage levels.

It is apparent that although an increase in dose enables more iron to be absorbed by the normal rat, the absorption from each additional milligramme of iron administered decreases as the dose increases. This is shown in Table III. The progressive decrease is more marked in the second experiment, where the absorption from 10·069 milligrammes was even less than from 5·069 milligrammes administered. This resulted in a negative figure for the increase in absorption per milligramme increase in dose; but this observation is not significant.

Within the limits of experimental error, the distribution of the absorbed iron in the blood, liver and spleen is uniform, and not dependent on the dose of iron administered or the amount absorbed. This is shown in Tables I and II, for all the series. It is consistent with the hypothesis that in the presence of normal hæmopoietic function the absorbed iron is distributed between the blood and the tissue stores in the same proportion as the total iron content of the blood and the stores (Finch *et alii*, 1949). As might be expected, there was some variation in different animals, but there was no relationship between the percentage of absorbed iron in the liver and the total amount which was absorbed.

DISCUSSION

The results obtained in these experiments on non-anæmic animals are similar to those reported by Hahn *et alii* (1940) on anæmic dogs. It appears, therefore, that the percentage absorption of iron decreases with increasing dosage, irrespective of the actual amount absorbed. When an animal is iron-deficient, large amounts of iron are absorbed from the gastro-intestinal canal (Hahn *et alii*, 1943) and anæmia *per se* results in increased absorption (Kaldor, 1954).

The range of iron dosage used in the experiments was selected because the largest dose (10·069 milligrammes) is slightly greater in relation to the weight of the animal than the corresponding therapeutic dosage used in man. The other doses are comparable with those recommended by various clinicians. One of the difficulties of oral iron therapy is that all iron compounds sometimes produce gastro-intestinal irritation and this has resulted in the

TABLE II

The Utilization of Ferrous Iron Administered Orally to Rats

Observation	Series					
	I	II	III	IV	V	VI
Amount of iron administered (milligrammes)	0·07	0·57	1·07	3·07	5·07	10·07
Number of rats	4	5	5	5	5	5
Mean weight (grammes)	324·0	365·0	371·0	371·0	369·0	353·0
Total iron absorbed from dose: mean ± standard error[1] (milligrammes)	0·007±0·003	0·029±0·005	0·043±0·010	0·098±0·018	0·150±0·011	0·142±0·028
Percentage of iron absorbed (mean)	10·1	5·1	4·0	3·2	3·0	1·4
Percentage of absorbed iron in blood (mean)	87·3	87·6	86·8	89·8	83·0	85·7
Percentage of absorbed iron in liver (mean)	9·9	7·7	8·2	7·5	17·0	12·5
Percentage of absorbed iron in spleen (mean)	2·9	4·7	5·0	2·7	0·0	1·8

[1] Standard error of the mean is obtained from $\frac{\sigma}{\sqrt{n-1}}$ where n is the number of observations.

TABLE III

Changes in Absorption of Iron with Increasing Dosage

Experiment I. Ferric Iron Administered

Dose (milligrammes)	0	0·025	1·025	3·025	5·025	10·025
Amount absorbed (milligrammes)	0	0·010	0·077	0·182	0·320	0·491
Increase in absorption		0·010	0·067	0·105	0·138	0·171
Increase in absorption per milligramme increase in dose		0·400	0·067	0·053	0·069	0·034

Experiment II. Ferrous Iron Administered

Dose (milligrammes)	0	0·069	0·569	1·069	3·069	5·069	10·069
Amount absorbed (milligrammes)	0	0·007	0·029	0·043	0·098	0·152	0·142
Increase in absorption		0·007	0·022	0·014	0·055	0·054	—0·010
Increase in absorption per milligramme increase in dose		0·101	0·044	0·028	0·028	0·027	—0·002

use of colloidal iron preparations which can be injected parenterally. The larger the oral dose of an iron preparation, the greater is the risk of producing gastro-intestinal irritation. In view of the evidence, obtained in anæmic dogs and non-anæmic rats, that increased dosage is not followed by proportionately increased utilization, there seems to be little reason for massive iron dosage.

In these experiments, more ferric than ferrous iron was absorbed at all corresponding dosage levels, the amounts being in the approximate ratio of 2 : 1. The relative absorption of the two forms was investigated in dogs and humans by Moore *et alii* (1944). They found that the dog absorbed approximately equal amounts of the two forms, whilst both normal and iron-deficient humans absorbed between 1·5 and 10 times as much ferrous as ferric iron. Austoni and Greenberg (1940) reported that rats absorbed both forms to the same extent. No adequate explanation has yet been offered for these species differences.

SUMMARY

In two experiments performed with ferric and ferrous iron, groups of fasting rats were given single doses of radioactive iron by stomach tube. The amounts of iron given to the various groups corresponded proportionately to the range of therapeutic dosage used in man. After three weeks the radioactivity present in the blood, liver and spleen was measured and compared with that given in the dose. It was found that as the dose increased, the amount of iron absorbed also increased, but the percentage absorbed decreased. Therefore the effect of incremental increases in dosage progressively diminished. At all dosage levels, more ferric than ferrous iron was absorbed.

ACKNOWLEDGEMENTS

The authors would like to thank Professor H. Messel for permitting the radioassay measurements to be made in the School of Physics, and they are grateful to the Nuclear Research Foundation within the University of Sydney for the provision of the radiometric equipment.

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CLINICAL FEATURES OF CERVICAL SPONDYLOSIS[1]

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During the past five years, increasing attention has been paid to abnormalities in the cervical part of the spine as the cause of neurological symptoms, though the first mention of spondylosis as a cause of paraplegia was made by Strümpell as early as 1888. Brain, Northfield and Wilkinson (1952) gave an extensive review of the literature and described 45 cases of their own, in 38 of which the spinal cord was compressed. Frykholm (1951) published a monograph with a comprehensive account of cervical disc degeneration, but dealt mainly with the clinical manifestations of nerve root compression. More recently, Symonds (1953) stressed the vulnerability of the spondylotic spine to trauma, while Pallis, Jones and Spillane (1954) pointed out that extensive radiological evidence of cervical spondylosis might occur in the absence of neurological symptoms or signs.

Brain (1948) indicated that herniation of the *nucleus pulposus*, whether traumatic or spontaneous, was nosologically different from the disc protrusions in cervical spondylosis. In the latter condition, the intervertebral disc has undergone degenerative changes which have caused osteophytic reactions in the adjoining vertebræ, and these osteophytes may protrude either into the spinal canal or into the intervertebral foramen. The protrusion may in time become calcified and represented by a bony ridge. Frykholm, who also distinguishes between the true nuclear herniations and the degenerative annular protrusions, points out that calcification may occur in both, so that in the chronic stage it becomes impossible to determine how they have started.

The neurological disturbances will depend largely on the site of the protrusion, which may be (i) dorso-medial, producing unilateral or bilateral cord compression, (ii) dorso-lateral, compressing the spinal nerve root against the lateral part of the vertebral lamina, and (iii) intraforaminal, compressing the nerve root against the articular processes (Figure I). As is to be expected, two or all three of these types are not infrequently combined.

The neurological symptoms may therefore be (i) radicular, or (ii) the result of cord compression, or (iii) a combination of both.

We intend to review a series of 40 patients, most of whom were examined at the Northcott Neurological Diagnostic Centre during the past three years, and propose to discuss them under two separate headings of (i) radicular syndromes and (ii) spinal cord syndromes.

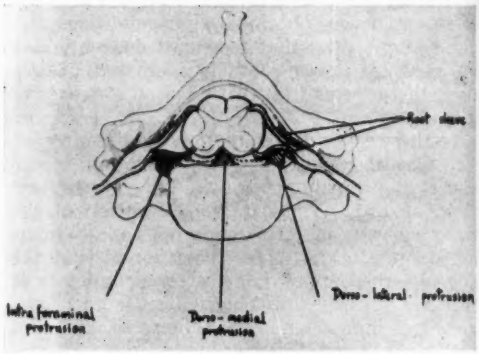

Figure I
Adapted from Brain (1954*a*)

Radicular Syndromes

Sex Incidence

In our series there were 23 patients in the radicular syndrome group, 19 males and four females. The sex incidence in this group is probably not representative of the general population, as the patients attending the Centre for investigation are predominantly male.

Age Incidence

The youngest patient in this series was aged twenty-six years, and the oldest seventy-two years, and the cases were distributed among the various age groups as follows: under forty years, six; forty-one to fifty years, six; fifty-one to sixty years, eight; sixty-one to seventy years, two; over seventy years, one.

[1] Received on January 23, 1956. Read at a meeting of the Section of Orthopædics, Australasian Medical Congress (British Medical Association), Ninth Session, Sydney, August 20 to 27, 1955.

Relationship to Trauma

Twelve patients gave no history of significant antecedent injury to the neck, but the remaining 11 recalled some trauma to the cervical part of the spine. In three of these cases there was a definite history of injury, and in each this had been sustained within six months prior to the appearance of symptoms. In the remaining eight cases, the history of trauma was less definite, and in all these cases whatever injury had been sustained had taken place more than five years before symptoms began. In some cases the symptoms and signs had been precipitated by and closely followed on a local injury, and X-ray examination had disclosed spondylotic changes present obviously for some considerable time before the injury.

Trauma, therefore, while not actually initiating the bony degenerative changes, may have an important role in precipitating clinical manifestations, a point which has been recently elaborated by Symonds (1953).

CASE 32.—Ten days before examination, this patient, a male, aged forty-three years, was struck on the back of the head and neck by a bag of sand which had fallen from about 25 feet. He was unconscious for several minutes, and on recovery of consciousness complained of severe pain at the back of the neck, accompanied by stiffness. Six days later he complained of intensely severe paroxysms of pain radiating over the left side of the neck to the left shoulder, acutely aggravated by movements such as walking, or by head movements. He also complained of recurrent paræsthesiæ over the left deltoid region and in the tips of all the left fingers. Examination showed that there was no local wasting in either upper limb, there was normal power in all movements, there was no sensory impairment and the reflexes were normal and equal. The head was held rigidly and inclined to the left shoulder, and there was pronounced limitation of all neck movements, especially of extension. Manual traction on the neck with the patient seated produced immediate relief from his paroxysms of pain radiating to the left shoulder. Plain X-ray films showed calcification anterior to the bodies of the fourth, fifth and sixth cervical vertebræ, and disc space narrowing at the fourth and fifth, fifth and sixth and sixth and seventh spaces. He obtained immediate relief of his acute pain after the application of continuous neck traction while in bed, but six months after his injury he still had a slight persistent ache at the back of the neck.

CASE 21.—A man, aged fifty-two years, with no previous history of injury or neurological illness, was working under the dashboard of his motor-car in June, 1949, when another vehicle ran into the car. He was thrown up against the windscreen, and his neck became hyperextended and his trachea was cut. He was detained in hospital for a fortnight after this injury and on discharge became aware of weakness at the left shoulder. This progressed, and within a few weeks he noticed twitching in the muscles about the left shoulder, and wasting of these muscles. This weakness and wasting persisted, and during 1953 he developed pain in the left arm, and muscular twitchings spread to the muscles of the left side of the chest. On physical examination of the patient there was considerable wasting of the left deltoid and brachioradialis, and slight wasting of the biceps, triceps, spinati and *pectoralis major*. Fibrillation was seen in all these muscles. There was considerable weakness of the wasted muscles, but power in the left forearm and hand was normal. Superficial sensation was impaired over the entire left arm and left side of the chest from the fourth cervical to the fourth thoracic dermatomes. All tendon reflexes in the left arm were depressed, while those in the lower limbs were normal, and the plantar responses were flexor. There was some tenderness and restriction of movement of the cervical part of the spine. The cerebro-spinal fluid was entirely normal, the protein content being 45 milligrammes per 100 millilitres, and a plain X-ray film of the cervical part of the spine was reported as normal; but the myelogram (Figures II and III) revealed a pronounced indentation in the column at the cervical disc levels from the third to the seventh cervical vertebræ, maximal at the fifth and sixth cervical vertebræ, where the column was completely interrupted on the left side, and the root sheath did not fill. In view of the multiple disc involvement, operation was not advised, and he was treated with a cervical collar with only slight improvement.

FIGURE II

Antero-posterior myelogram of a male patient, aged fifty-two years, who one month after an extension injury to the neck developed sensory impairment, weakness and wasting in a left fourth, fifth and sixth cervical distribution. Multiple mid-line disc protrusions from the second and third cervical to the seventh cervical and first thoracic spaces

Pathology

Frykholm (1951) describes thickening and opacity of the dural sac around the nerve root, which he calls root sleeve fibrosis, as the pathological lesion causing the radicular symptoms. He mentions also that the shortening of the cervical part of the spine resulting from the degenerative spondylosis produces an alteration in the direction of the emerging

FIGURE III
Same patient as Figure II; lateral myelogram

spinal roots, which may be compressed against the borders of the exit foramina without osteophytic spurring encroaching on these. The disc degeneration further produces an apposition of the transverse processes with narrowing of the intervertebral canal, so that roots may be subjected to pressure by intervertebral foramina which are not the seat of bony spurs.

Symptoms and Signs

The duration of symptoms when the patient was first examined varied from four days to twelve years. Some of these patients present almost as an "emergency", with an intense brachialgia acutely aggravated by even minor neck movements or any straining effort. On the other hand, the pain may be less severe, more spontaneously remittent and less demanding of immediate attention, with the result that several years may elapse before the patient presents himself, and then he does so mainly because of increasing loss of function in the affected limb. Symptoms involved both upper limbs in five cases, but in the remaining 18 cases the disability was unilateral (11 left-sided, seven right-sided), and the side involved bore no relation to the dominant handedness of the particular patient.

The predominant symptom was pain. This varied from a paroxysmal, intensely severe neuralgia radiating from neck to fingers, to a much less severe, recurrent, dull ache in part or all of this territory. The pain in the more severe and acute cases was usually much accentuated by sudden movements of the neck, and also by coughing, sneezing or straining at stool. In most cases the pain in its distribution could not clearly be related to any discretely radicular zone. Distribution of the pain is not always strictly dermatomal, but may radiate into a wider territory, which Brain explains by the wider distribution of the myotomes and sclerotomes.

In all but three cases the pain was accompanied by paræsthesiæ in the form of numbness and tingling or burning sensations, most commonly referred to the fingers, sometimes remaining in a discrete dermatomal area. These paræsthesiæ, especially in the more acute cases, were, like the pain, readily aggravated by straining efforts.

CASE 26.—A minister of religion, aged forty years, suddenly experienced an aching pain in the left arm and the radial part of the left forearm while straining at stool in January, 1955. A similar pain had occurred intermittently since then, and was followed by a feeling of numbness along the left forearm and the radial three fingers of the left hand. It was invariably brought on by straining at stool or by turning his neck to the left side. During March, 1955, tingling occurred in the same distribution, but there was no significant weakness or clumsiness of the left hand. Physical examination revealed minimal wasting of the left thenar eminence and slight hypoalgesia along the left forearm in a sixth cervical distribution. There was no limitation of neck movement, but rotation of the cervical part of the spine to the left produced paræsthesiæ in the left arm. Oblique projections of the cervical part of the spine showed a well-defined osteophytic spur projecting into the left fifth to sixth cervical exit foramen. Continuous neck traction for a fortnight produced no alleviation of his symptoms, and a myelogram revealed an interruption of the column of contrast medium at the fifth and sixth cervical vertebræ on the left side, with failure of root sheath filling, and a slight indentation at the sixth and

seventh cervical level. At laminectomy in June, 1955, the left sixth cervical nerve root was found stretched over an osteophytic spur and the roof of the exit canal was decompressed, with rapid relief of all his symptoms.

Objective sensory impairment occurred in 12 cases out of the 23, and was often very mild, being confined to relative impairment of two-point discrimination, or of postural sensibility in the fingers, and localized to particular segmental areas. The individual dermatomal regions in the hand appeared to be involved with equal frequency over this series of cases.

Thirteen patients in the present series showed both muscle wasting and weakness; two patients showed slight weakness, unaccompanied by wasting; and the remaining eight patients complained of no weakness, nor was any observed. Impairment of the finger movements of fingers and hands was, as might be expected, the most common motor disability compalined of; but weakness and muscle atrophy occurred in all the radicular segments of the upper limb with approximately equal frequency.

Loss or diminution of various combinations of tendon reflexes in the upper limbs occurred in nine of the present series, while in the remaining 14 the tendon reflexes were classified as normal. The finding of depressed tendon reflexes seemed to bear no constant relationship to the duration of symptoms.

In 16 of the present series there were varying degrees of restriction of movement of the head and neck. In the more acute and recent cases in which the brachialgias were more intense, there was actually spasmodic fixation of the head and neck in a particular position, movements from which would severely accentuate the pain. As has been previously mentioned also with reference to these more acute and recent brachialgias, coughing and straining exerted a considerable aggravating influence on the pain. Rotation of the chin to the affected side frequently produced pain down the arm, and it was sometimes a helpful therapeutic test during the examination to exert manual traction on the head with the patient sitting in a chair; this manœuvre on several occasions produced immediate relief from pain in those suffering from acute brachialgia accompanied by spasmodic immobilization of the neck.

X-ray Findings

The radiographic findings may be classified under the following two main headings: (i) The presence of disc space narrowing at one or several levels and usually accompanied by sclerosis of the adjacent vertebral margins with anterior or posterior lipping, or both (Figure IV). (ii) Evidence of encroachment on the exit foramina, again at one or several levels, by posterior osteophyte formation (Figure V). Specialized radiographic technique is important in this connexion, and it is usually wise to take lateral projections in flexion and extension, as well as an antero-posterior and both oblique projections. In some cases the

FIGURE IV

Plain lateral view of the cervical part of the spine of a man, aged fifty-four years, showing pronounced disc space narrowing at the fifth and sixth cervical level, with reactive changes in the adjoining vertebral bodies

normal cervical lordosis is exaggerated, while in others there is straightening of the normal cervical curve, or even a mild kyphosis.

Plain X-ray abnormalities were encountered in all but two of this series. These abnormalities were as follows: disc space narrowing at a single level (six cases); narrowing of disc spaces at several levels (15 cases); posterior osteophytic encroachment on the exit foramina (18 cases). The two patients who had normal plain X-ray findings both showed definite abnormalities on myelographic examination (Figures VI and VII). Myelography is always essential if surgical intervention is contemplated, because the myelogram may reveal

protrusions into the spinal canal at levels in addition to that suggested by the plain X-ray film. Brain (1954*a*) pointed out that congenital abnormalities of the cervical part of the spine, such as fusion of two or more vertebræ, added

FIGURE V

Oblique view of the cervical part of the spine, showing encroachment on the sixth and seventh cervical exit foramina by osteophytic spurs

to the strain upon neighbouring discs, and were more frequently encountered among patients suffering from cervical spondylosis than in a group of controls. No such congenital abnormalities were found in our series.

Myelography

Myelograms were taken in five cases, and revealed interruption of the column of contrast medium at the levels suspected clinically or from the plain X-ray findings. This interruption was usually most pronounced on the affected side in unilateral cases. In the two cases in which the plain X-ray findings were normal, myelograms were taken on the basis of clinical findings, in one revealing a definite "cut out" in the contrast medium opposite the sixth and seventh cervical vertebræ and in the other a complete interruption of the column at the level of the fifth and sixth cervical vertebræ.

In the majority of these cases myelography was not required because the diagnosis could be adequately reached from a combination of the clinical evidence and the plain X-ray

FIG. VI

A normal plain lateral radiograph of the cervical part of the spine in Case 30; the patient presented with pain and paræsthesiæ in the left arm and weakness and clumsiness of the left hand

findings. Myelography is indicated in those cases in which there are no plain X-ray changes in spite of a persistent radicular lesion, or in those cases in which operation is contemplated.

Differential Diagnosis

The most frequent diagnostic problem in this radicular group is the differentiation from other causes of cervico-brachial pain and paræsthesiæ. The syndrome of so-called acro-paræsthesiæ may present special difficulties; this may be defined as unpleasant and frequently painful tingling sensations occurring in one or both hands, most commonly in middle-aged women, and chiefly at night, frequently waking the patient and passing off within one or two hours of rising. This syndrome is essentially one of irritation of sensory fibres, and it may be extremely difficult to determine at which level such irritation may be arising. It may result from cervical spondylosis, or from a costo-clavicular syndrome or from compression of the median nerve in the carpal tunnel. Each of these three conditions may present with brachial pain and paræsthesiæ, and a proper clinical examination is highly important in differentiating the cause, especially as radiological evidence of cervical spondylosis may be present but unrelated to a coexisting cause of symptoms at another level.

CASE 36.—A female patient, aged fifty-four years, had for six years complained of intermittent pain and stiffness at the back of the neck, accompanied by sharp pain radiating down the inner border of the left arm. For two years she had been troubled by nocturnal attacks of numbness and burning pain in the left thumb and radial three fingers, and for four months she had noticed progressive clumsiness of the left hand. There was no history of past injury. Examination of the patient revealed slight wasting and weakness of the left thenar muscles, and hyperæsthesiæ to pinprick over the left thumb, index and middle fingers and over the lateral half of the ring finger. Percussion over the left carpal tunnel produced painful paræsthesiæ in the left thumb, index and middle fingers. There was tenderness to mid-line pressure posteriorly over the cervical part of the spine with moderate limitation of flexion and extension of the neck. Plain X-ray films revealed considerable disk space narrowing and reactive changes at the fourth and fifth cervical level. A clinical diagnosis was made of cervical spondylosis with the more recent onset of a left carpal tunnel syndrome. The nightly application of an anterior plaster splint to the left wrist immediately abolished her nocturnal attacks of pain and paræsthesiæ in the left hand. She still complained of persistent pain in the neck, but this was relieved by the application of a collar. She has been free of nocturnal attacks of pain and paræsthesiæ in the left hand ever since the application of the splint.

In the last few years it has become increasingly apparent that lesions at carpal tunnel level may produce diffuse brachialgia radiating as far as the shoulder or side of the neck (Kremer, Wilson, Golding and Gilliatt, 1952). The persistent localization of paræsthesiæ to the median nerve area of the palm and fingers, the occurrence of localized muscle wasting and weakness in the hand, again in the territory of the median nerve supply, and the elicitation of paræsthesiæ in the affected fingers by percussion over the carpal region should all help in the separation of these distal medial nerve lesions from this group.

The costo-clavicular syndrome presents similar difficulties in diagnosis, but the absence of discrete localization of sensory signs or

FIGURE VII

Myelogram of the same patient as in Figure VI, showing a cut-out in the column of contrast medium opposite the sixth and seventh cervical disc space on the left side

symptoms to the median nerve area, the close relationship of symptoms to downward traction on or hyperabduction of the arm, and the ready obliteration of the radial pulse by similar manœuvres all point towards this particular region.

Another interesting problem from the point of view of differential diagnosis is the coexistence of pain in the shoulder and arm, generalized restriction of shoulder movements and radiological evidence of cervical spondylosis.

Opinions are divided as to the role played by periarticular abnormality at the shoulder in the production of this syndrome. There is no doubt that in some such cases cervical traction is followed by relief from pain, and the attainment of an increased range of movement at the affected shoulder. One may only add in this regard that cervical traction (preferably continuous traction, with the patient in bed) may be a useful therapeutic test in distinguishing between a cervical or periarticular cause of such a syndrome.

The other lesions which have to be considered in the differential diagnosis of a motor or sensory disturbance in one upper limb include ulnar neuritis, paralytic brachial neuritis, syringomyelia and motor neuron disease. Again, it may be stressed that it is only after careful clinical examination that one should attempt to decide whether the radiological evidence of cervical spondylosis so commonly encountered in this age group is significant with relation to the particular case.

Treatment

In the great majority of cases in the present series, the patients were treated along conservative lines. According to the nature of the disability, conservative treatment naturally falls into one of the two following groups:

1. When the presenting symptom is an intense brachialgia of recent onset, the immediate relief of pain is the prime object. In our experience, cervical traction has been a satisfactory method of relief. In the more severe cases, continuous cervical traction should be applied, with the patient in bed; after the subsidence of the acute pain, a collar is fitted and the patient is allowed up. In this group, however, if the pain is severe and persistent, unresponsive to cervical traction and associated with plain X-ray findings of posterior encroachment at a single and appropriate level, operative decompression may be necessary. The general opinion in the literature cited is that operation is not advisable in the older age group beyond the age of forty-five to fifty years. Operation was performed on one patient of our series, with immediate relief of symptoms.

2. When the patient's disability is a relatively long-standing impairment of motor or sensory function in the upper limb, operation is not likely to be of help, and the results of conservative management are often also disappointing. One may only hope that by partial immobilization in a collar, further damage to the affected nerve roots may be lessened or prevented.

SPINAL SYNDROMES

Sex Incidence

Twelve patients in our series presented with signs pointing primarily to cord compression. Six of these were male and six female.

Age Incidence

The youngest patient in this series was aged forty-nine years and the oldest seventy-six, and the distribution in the various age groups was as follows: forty-five to fifty years, three; fifty-one to sixty years, four; sixty-one to seventy years, four; over seventy years, one.

Relationship to Trauma

Eight patients in this group could not recall any definite injury to the neck or head. Two reported such an injury more than five years preceding the onset of their symptoms, and two had sustained trauma to the neck within two months of the appearance of their disability.

As Brain *et alii* (1952) have pointed out, the actual incidence of trauma is probably higher than one-third, and it is conceivable that some of the patients had forgotten minor injuries to the neck in the preceding years which could have initiated the degenerative process. In one patient, pain in the left arm and stiffness of the neck occurred within a few days after a fall from a horse, though symptoms of spinal cord compression developed only ten years later, during which time cervical pain and stiffness had been persistent. In another case, symptoms began almost immediately after a torsion injury of the neck, though there was radiological evidence of preexisting cervical spondylosis.

CASE 31.—This man, aged fifty-six years, had had no significant past illness and gave no history of previous neck injury. One month prior to examination he had been suddenly grasped in a head lock by one of his work-mates, and his head was jerked backwards in the process. He immediately "felt something click in his neck", and within a few minutes noticed a numb feeling in the left arm, extending down to the finger tips and upwards to the left side of the back of the neck and scalp. Within an hour the whole left arm became useless, and then made a gradual recovery over several weeks. For the first few days he had an aching pain down the left arm from shoulder to fingers. Examination of the patient one month after the injury revealed slight weakness of shrugging of the left shoulder, and moderate weakness of movements at the left shoulder, elbow, wrist and fingers. The left supinator jerk was absent, and the left biceps jerk considerably diminished. There was impairment of superficial sensation to pain and temperature (but not to touch) over the left side of the neck and left upper limb in the second to fifth cervical area. This area of sensory loss was sharply demarcated and dissociated in type. There was moderate generalized restriction of all neck movements. Plain X-ray films

of the cervical part of the spine showed well-marked disc space narrowing at the fifth and sixth cervical level. The cerebro-spinal fluid was normal in all respects, with a protein content of 40 milligrammes per 100 millilitres, on the upper limit of normal. He made a gradual improvement over the next six months, but during this time had two further attacks of paræsthesia and loss of power in the left arm, each lasting about half an hour. His clinical picture indicated an acute intramedullary cervical lesion immediately following a torsion injury to the neck.

Symonds (1953) demonstrated the interrelation of trauma and cervical spondylosis in cord compression, and cited two cases in which symptoms began immediately after tonsillectomy, and two after other operations to the head. He suggested that hyperextension of the neck during anæsthesia might have been the factor producing these serious symptoms in patients predisposed by degenerative changes in the cervical part of the spine.

Pathology

Brain *et alii* (1952) were able to secure post-mortem examinations on six of their patients, and in general found flattening of the cervical part of the cord opposite the protruding discs and in some cases gross softening with obvious long tract degeneration below the level of the lesion. This they termed myelopathy, or in advanced cases myelomalacia. They considered that these pathological changes were produced not only by cord compression from the protruding bar, but also by vascular impairment resulting from encroachment on the radicular arteries in the narrowed spinal foramina, and direct compression of the anterior spinal artery by a mid-line protrusion. It was further suggested that even the vertebral artery might be compressed in its canal by lateral disc protrusions, with further vascular impairment. Atherosclerotic arteries with an already narrowed lumen are even more prone to this damage, and the predominant incidence of this syndrome in the later age groups would support the significance of vascular factors. It follows from these pathological considerations that cervical decompression in elderly patients can at best only relieve the compressing factor without affecting the vascular impairment. In some cases of cervical disc degeneration an abnormal mobility of the intervertebral joints results, which increases the liability to repeated trauma.

In a series of post-mortem studies on spinal cords damaged by cervical spondylosis, Mair and Druckman (1953) found that the injury involved principally the anterior horns, the lateral columns and the anterior part of the dorsal columns (Figure VIII). They noted that the lesions were not of uniform severity, and stressed the importance of a vascular factor in their pathogenesis, also noting that the distribution of the degenerative changes in their cases was almost identical with the field of supply of the anterior spinal artery. The anterior spinal artery will suffer the effects of compression not only on the surface of the cord, but also in its branches throughout the cord, and it is upon these finer distal branches that the compressive forces will exert the most effect. Mair and Druckman (1953) have also observed damage to the arterial walls in the region of the compression, which is probably a further factor contributing to the ischæmic myelopathy.

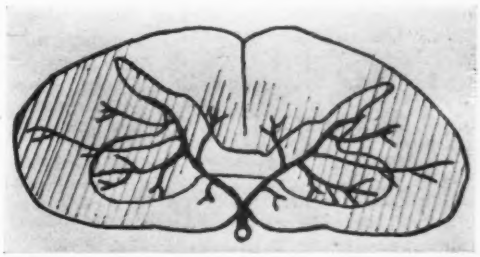

FIGURE VIII

In this diagram the shaded areas show the distribution of the cord lesions in the segment of maximal compression, and their relation to the anterior spinal artery and its branches. (Adapted from Mair and Druckman, 1953)

Symptoms and Signs

The shortest duration of symptoms before the patient presented for examination was one month, and the longest eleven years. The patient with the short history (Case 31) has been referred to above. In the majority of cases the onset of symptoms was gradual, and either involved the lower limbs with a slowly progressive weakness and stiffness, or affected initially the nerve roots to the upper limbs causing pain and paræsthesiæ from a lateral protrusion before the mid-line disc produced spinal compression. The symptoms in the upper limbs may, of course, be produced either by radicular or by cord compression. Eleven of the 12 patients in this series had either symptoms or signs referable to both the upper and the lower limbs. In one, symptoms and signs were confined to the left upper limb and the chest, in a second there were only subjective symptoms without confirmatory signs in the upper limbs, while another had increased tone

and tendon reflexes in one upper limb without subjective symptoms.

The symptomatology in this group was extremely varied, which may be expected from the fact that the disc protrusions may be single or multiple, and that lateral osteophytes may add radicular symptoms at one or several levels, unilaterally or bilaterally, to the cord picture.

The initial symptoms referred to the upper limbs in four cases and to the lower limbs in seven, and apparently affected both arms and legs simultaneously in one case.

Weakness, stiffness and unsteadiness of the lower limbs were the outstanding symptoms, and were either constant and steadily progressive or intermittent. In eight cases weakness involved both legs, and in three one leg only. Unsteadiness of gait was complained of in seven cases. Spasticity with increased tendon jerks was confirmed in both lower limbs of seven patients and in one lower limb in three, and either one or both plantar responses were extensor in 11 patients. Weakness of one arm occurred in four, and of both arms in another four, while wasting of the hands was observed in only two patients. Both upper limbs were spastic in two, and one only in one. Pain or paræsthesiæ in the arms or hands were complained of in all 12 cases, and occurred in the legs in only three. The tendon reflexes in the upper limbs were depressed or absent in four patients, and one had an inverted radial supinator response. Impairment of sphincter control was complained of by only two patients. Neck movements were restricted or painful in five, and one patient mentioned shock-like sensations on flexing his neck. Muscle fasciculation was observed in two patients, but was rather coarse and not of the fine continuous variety usually seen in motor neuron disease. Two patients in this series had associated disc protrusions in the lumbo-sacral region, which produced added clinical signs.

From this analysis it can be seen that the symptomatology is protean, and that it can simulate quite a variety of organic neurological disorders.

X-ray Findings

The radiographic appearances are similar to those described earlier during the discussion of the radicular components of cervical spondylosis. They are again characterized by disc space narrowing with reactive changes in the adjoining bone margins.

All 12 patients had abnormalities in the plain X-ray films. In six of them only one disc level was involved, and in six several disc spaces were narrowed. Myelograms were taken in six cases. In two of these it revealed abnormalities at a single level only, in one of which there was a complete hold up at the fourth and fifth cervical level (Figure IX).

FIGURE IX

A lateral view of the cervical part of the spine of a female patient, aged fifty-one years (Case 33), with a three months' history of stiffness and unsteadiness of gait, followed by paræsthesiæ and clumsiness in both hands and impairment of sphincter control. Clinical examination in this case revealed early spastic tetraplegia, with slight objective sensory loss in the fingers. This skiagram shows disc space narrowing and reactive bony changes at the fourth and fifth, fifth and sixth, and sixth and seventh cervical levels. A cisternal myelogram revealed an almost complete hold-up opposite the fourth and fifth cervical disc space, and operative decompression was followed by rapid and almost complete recovery

In the remaining four there was interruption of the column of contrast medium at several levels, and it may be significant that in two of these the plain X-ray film had shown only narrowing of a single space (Figures II and III).

The cerebro-spinal fluid was examined in six cases, and it was normal both manometrically and chemically in all, though the protein value was between 40 and 50 milligrammes per 100 millilitres in three cases. The normal Queckenstedt reaction in the presence of spinal compression has also been noted by other authors, and is probably explained by the fact that the obliteration of the canal is only partial in the majority of cases.

In general, myelographic appearances in this group do not differ significantly from the radicular group. Again, posture is of some importance, and extension of the neck during the taking of the lateral film may accentuate indentation of the column of contrast medium which might otherwise be overlooked.

Differential Diagnosis

As has been mentioned, the varied clinical picture of cord damage resulting from cervical spondylosis may simulate almost any disease affecting the spinal cord, and the differential diagnosis from subacute combined degeneration, disseminated sclerosis, motor neuron disease, syringomyelia, spinal syphilis or spinal cord tumour is often extremely difficult.

One patient in this series (Case 40) was suspected of having subacute combined degeneration when he was first examined.

CASE 40.—A clerk, aged sixty-one years, with no recollection of any injury to the cervical part of the spine, presented in March, 1952, complaining of deterioration of his handwriting for five years and gradually progressive weakness of his legs with some unsteadiness for three years. His hands had become progressively more clumsy since 1948. During 1949 he first noticed some weakness and stiffness of the right leg, and within a few months the left leg was similarly involved, and he frequently felt unsteady. He was quite unable to walk more than half a mile, and could not run. In 1950 he first experienced numbness and paræsthesiæ of the fingers of both hands. Physical examination confirmed the presence of a spastic weakness of both lower limbs, with increased tendon jerks and bilateral extensor plantar responses. At that stage there was no wasting of the intrinsic muscles of the hands, but rapid repetitive movements of the fingers were slowly and clumsily performed. There was some diffuse hypoalgesia of both arms below the elbows, and vibration sense was impaired in both lower limbs, the left more than the right, while the sense of passive movement remained normal. It was thought on clinical grounds that he was suffering from subacute combined degeneration, but a full blood count and the results of a fractional test meal examination were entirely normal. The cerebro-spinal fluid was normal; it did not react to the Wassermann test and the Lange curve revealed no abnormality. A plain X-ray film of the cervical part of the spine showed some disc space narrowing at the fifth and sixth cervical level. Conservative management was advised, but the patient was not satisfied with his progress and sought admission to another hospital, where myelography was performed in May, 1952; this revealed definite indentation of the column of contrast medium at the fifth and sixth cervical level. At laminectomy a transverse ridge was found at the level of the fifth and sixth cervical disk space. The *ligamenta denticulata* were cut and the dura overlying the ridge was incised, and an attempt was made to obtain some tissue from this bony ridge. The patient's condition deteriorated rapidly after this operation, and he developed progressive wasting of the intrinsic muscles of the hand, extending even to the forearm muscles, with abolition of the tendon jerks in the upper limbs. The spastic weakness of his legs also progressed, and impairment of sphincter control developed. He has been confined to bed for the past year, and experiences occasional flexor spasms of the legs.

Two patients had been diagnosed as suffering from disseminated sclerosis, though closer analysis of their symptoms and the myelographic findings established the correct diagnosis. Case 24 will exemplify this difficulty.

CASE 24.—An accountant, aged fifty years, had an episode of blurring of vision at the age of thirty-five years which gradually developed into a horizontal diplopia continuing for some three years. He was examined by an eye specialist, who still had notes of the case, and found no paresis of any ocular muscle, but was able to correct the diplopia with prisms, which were gradually reduced in strength. It was thought that this diplopia might have been due to an orthoptic breakdown, and it never recurred after the age of thirty-eight years. It was not associated with any weakness or sensory or sphincter disturbance. Thirteen years later, in 1953, he had an episode of sudden weakness of both legs, which lasted for some four weeks, and was accompanied by paræsthesiæ in the feet. Some weakness of the legs has persisted ever since then, but occurs only on strenuous physical exertion, such as gardening or walking long distances, and recovers immediately with rest. During 1954, the patient began to notice numbness and tingling of the fingers of both hands, which also became clumsy. There has been no sphincter disturbance during the course of this illness. At the end of 1954 he first noticed stiffness of the neck and a clicking noise on moving the neck to either side and pain on turning the neck to the right. Physical examination revealed no abnormality in the optic discs or fundi, and no nystagmus or diplopia. Coordination in the upper limbs was normal, and the finger-nose test was steadily performed without any tremor. There was a slight weakness at the right ankle, but tone and power in the lower limbs was otherwise normal. The tendon reflexes were normal except for diminution of the right ankle jerk due to an associated lumbo-sacral disc protrusion; the abdominal reflexes were brisk and equal, and both plantar responses were flexor. Pressure over the cervical part of the spine produced pain, and cervical movements were restricted. The plain X-ray film revealed only some straightening of the cervical part of the spine and slight posterior lipping at the sixth and seventh cervical level, but the myelogram indicated mid-line disc protrusions at the fifth and sixth and the sixth and seventh cervical levels, as well as a lumbo-sacral disc prolapse. Examination of the cerebro-spinal fluid (including the Lange colloidal gold curve) gave entirely normal results. He was treated along conservative lines and was reassured that he need not worry about the sinister diagnosis of disseminated sclerosis previously offered.

The patient in Case 15 presented with a clinical picture strongly suggestive of motor neuron disease, but had definite objective sensory impairment extending over the left limbs and trunk up to a level of the sixth cervical segment, which immediately threw doubt on this diagnosis.

FIGURE X

Oblique view of the cervical part of the spine in Case 15, showing osteophytic encroachment on the third and fourth, fourth and fifth and sixth and seventh cervical exit foramina

CASE 15.—This patient, a male, aged fifty-one years, gave a six months' history of progressive weakness in the legs and arms associated with muscular twitching in both upper limbs. After an injury to the left shoulder twenty-seven years previously he had noticed weakness and wasting of the muscles in the left arm. On examination, he now showed a minimal left Horner's syndrome, and coarse fasciculations in the muscles of both shoulder girdles and in both quadriceps; there was no local wasting. He had a shuffling, spastic gait. There was impairment of superficial sensation over the left leg, the left side of the trunk and left upper limb up to the sixth cervical level. Reflexes in the left arm were diminished, both knee jerks were exaggerated, and the left plantar response was extensor. Neck movements were full. Plain X-ray films of the cervical part of the spine (Figure X) showed osteophytic encroachment at the third and fourth, fourth and fifth, and sixth and seventh cervical exit foramina. The myelogram (Figures XI and XII) showed complete interruption of the column of contrast medium at the third and fourth cervical level, with indentations at all the lower disc levels. Examination of the cerebro-spinal fluid revealed no definite abnormality, but the protein content of 45 milligrammes per 100 millilitres was on the upper limits of normal.

The condition of the patient in Case 31 simulated syringomyelia, though his symptoms began almost immediately after a torsion injury to the neck; this case has been cited above.

As compression of the spinal cord is a causal factor in all these cases, a spinal cord tumour obviously comes to mind in the differential

FIGURE XI

Antero-posterior myelogram (Case 15), showing complete interruption of the column of contrast medium at the third and fourth cervical disc level, with indentations at all the lower disc levels

diagnosis, and for this reason myelography is indicated in a considerable proportion of cases. Case 31 was not unlike one of intramedullary tumour, had the history of injury been overlooked. One patient (Case 29) presented with spastic weakness of the left leg, which was dramatically relieved by laminectomy.

CASE 29.—A woman, aged forty-nine years, who recalled no injury to the neck, was referred early in 1954 with an eleven months' history of progressive weakness of the left leg and a dull ache in the left hip. She had no sensory symptoms and no sphincter impairment, and did not mention any pain in the neck. Physical examination confirmed the presence of spastic weakness of the left leg, and further revealed a moderately severe spastic weakness of the left arm. There was no wasting of the intrinsic muscles of the hand, and no objective sensory impairment. The tendon reflexes were increased in the left arm and left leg, and both plantar responses were extensor. Movement of the cervical part of the spine was restricted in all directions, but painless. The cerebrospinal fluid was normal manometrically and chemically, and did not react to the Wassermann test. Plain X-ray films demonstrated disc space narrowing at the fifth and sixth cervical level, and milder osteoarthritic changes in the lower dorsal and upper lumbar parts of the spine. Myelography revealed a mid-line filling defect opposite the fifth and sixth and the sixth and seventh cervical disc spaces. Laminectomy was performed in December, 1954, and transverse bars were found at the fifth and sixth and the sixth and seventh cervical levels. The *ligamenta denticulata* were divided and the cord was decompressed by removal of the laminæ, but no direct attack was made on the transverse bars. The weakness of her left arm and leg has decreased considerably since this operation, and she is now able to walk without the aid of a stick.

Gradually progressive paraplegia beginning during late middle age has presented a diagnostic problem for many years, and at one time used to be called "senile paraplegia". It would now appear that the majority of these cases were due to cervical spondylosis. The question then arises why only the lower limbs should be paralysed, or why there should be so little involvement of the ascending sensory tracts in many of these patients when the cord damage occurs at a cervical level. This seems to be explained by Mair and Druckman's (1953) pathological studies showing the maximal involvement of the pyramidal tracts due to vascular impairment in the territory of the anterior spinal artery. If the cord compression occurs below the fourth cervical level, the upper limbs will be spared a spastic weakness, while cord compression above this level can cause spastic quadriplegia.

The occurrence of radicular involvement presenting either as paræsthesiæ, pain or wasting in the upper limbs, combined with spastic weakness of one or both lower limbs, particularly in an elderly patient, should always lead one to suspect the diagnosis of cervical spondylosis.

Treatment

It is now thought by most neurologists that treatment should be along conservative lines in the majority of these cases. As several disc levels are involved in most cases, and as the condition occurs predominantly in the later age groups, in which atheromatous vascular degeneration may be expected, cervical decompression is not often helpful. Surgical interference may indeed aggravate the condition and produce complete paraplegia, the increased mobility of the neck after laminectomy adding further trauma to an already damaged cord.

FIGURE XII

Lateral myelogram (Case 15), showing the same as Figure XI

Spinal manipulation should also be avoided if we remember the precarious vulnerability of the spinal cord during the simple operative procedures mentioned above. Gentle and continuous neck traction may be helpful in some cases, followed by the application of a cervical collar in partial extension which should be worn for at least six months. It is now held that operation should be reserved for the patient aged under forty-five years with myelographic evidence of only single disc

involvement, and without degenerative arterial changes.

Three patients in this series were subjected to operation. Two, aged forty-nine and fifty-one years respectively, with a single disc protrusion, did very well and obtained considerable relief from all their symptoms. The third, aged sixty-one years, was subjected to operation at another hospital, and deteriorated considerably after his operation.

CERVICAL SPONDYLOSIS WITHOUT EITHER RADICULAR OR CORD INVOLVEMENT

The remaining five patients in our series presented with pain at the back of the neck or head and were found to have radiological evidence of cervical spondylosis, though neither symptoms nor signs of root or cord damage could be elicited. Four of these were male and one was female, and their ages ranged from forty to fifty-nine years. Four of these patients gave a history of trauma to the neck, five or more years before the onset of symptoms, while one could not recall any injury. In three of these cases the pain radiated into one or both shoulder regions, and three of them had severe restriction of their neck movements, which were also painful. In these cases, traction on the neck with the patient sitting in a chair often produces immediate and dramatic relief of pain in the neck and head.

CASE 2.—A housewife, aged forty years, was first examined in February, 1954, complaining of episodes of pain in the neck and stiffness at the back of the neck over the past ten years, and a constant pain at the right side of the neck, aggravated by turning the head to the right, for seven years. The pain was invariably brought on by turning the neck to the right and was usually relieved by straightening it again. She had sustained several falls from horses during her youth, and thought that she might have injured her neck in these. There were no symptoms pointing to radicular or cord involvement, and no abnormal neurological signs. The range of neck movement was severely restricted in all directions. Plain X-ray examination revealed gross disc space narrowing between the fifth and sixth cervical vertebræ with posterior lipping and an acquired obliteration of the disc space between the sixth and seventh cervical vertebræ. She was fitted with a cervical collar.

The plain X-ray films in all cases revealed pronounced disc space narrowing with both anterior and posterior lipping at several levels, but myelography, of course, was not performed in any of these (Figures XIII and XIV).

Our reason for including these five cases in this series is to show that advanced radiological abnormalities may occur in the cervical part of the spine and be identical with those seen in patients with radicular or spinal lesions, without, however, producing any such serious neurological disturbances. We must therefore be aware that cervical spondylosis, which is not uncommon after middle life, may be quite symptomless, and should not be misled into attributing the patient's symptoms to the X-ray changes without careful clinical assessment. If any doubt arises, myelography is advisable, and in general one cannot accept

FIGURE XIII

Lateral view of the cervical part of the spine, showing gross disc space narrowing at the fifth to seventh cervical level, with posterior lipping. The patient, a woman, aged forty years, complained of pain and stiffness in the neck radiating into the shoulders and occiput, but had no signs of either cord or root involvement

cervical disc protrusions as the cause of the patient's disease unless the myelogram demonstrates one or several disc protrusions causing a significant reduction of the spinal canal in the neck. Here again clinical accuracy and experience must take precedence over the simpler conclusions from the radiological investigations.

Pallis, Jones and Spillane (1954) took X-ray films of the cervical part of the spine of 50 hospital in-patients who were admitted with non-neurological conditions. All were over the age of fifty years. While 75% of these

patients had X-ray changes indicating narrowing of the cervical spinal canal, only 50% of them had any neurological signs, though very few complained of symptoms. Of these 50 patients, 75% showed narrowing of intervertebral foramina, but only 40% had any signs of radicular damage, which again was mostly symptomless. Pallis, Jones and Spillane conclude that involvement of the spinal cord

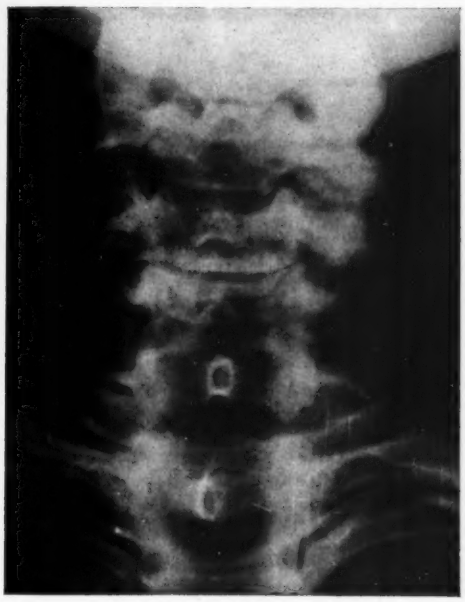

FIGURE XIV

Antero-posterior view of the cervical part of the spine, same patient as in Figure XIII

and nerve roots in cervical spondylosis may occur in a silent manner, and that objective neurological signs may precede the appearance of symptoms. These observations and the evidence of serious and distressing neurological complications resulting from cervical spondylosis stress the need for preventive measures. At present, we know only that special care must be taken with manipulation or extension of the spondylotic spine; but further avenues of prevention will merit serious research.

SUMMARY

The clinical features of 40 cases of cervical spondylosis have been reviewed. The radicular symptoms were distinguished from those resulting from spinal cord compression.

The radiological and myelographic findings in these cases have been described.

Mention has been made of the importance of trauma in producing neurological damage in patients with cervical disc degeneration.

Conservative treatment was advocated for patients above the age of fifty years, and for those with multiple disc involvement.

The radiological appearances of cervical spondylosis cannot be accepted as the cause of the patient's symptoms without appropriate clinical assessment.

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VASCULAR ANOMALY OF THE SPINAL CORD ILLUSTRATED BY THREE CASE REPORTS[1]

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THE delineation of cerebro-vascular malformations is now routine angiographic procedure, and the surgical excision of certain of these lesions has become a feasible undertaking. The early experience of this unit has already been reported (Moss, 1953). Unhappily, recent advance in knowledge of the symptomatology, pathology and management of central nervous vascular malformation stops short at the spinal cord. Little has been added since Wyburn Mason's monograph thirteen years ago, in spite of his assertion that with an increasing awareness of their existence, spinal vascular anomalies would prove far commoner than had hitherto been supposed.

Two reasons suggest themselves for the paucity of case reports. The first is the ease with which the diagnosis may be missed, and the second is the sense of futility which confronts the practitioner who knows that even when it is made nothing effective can be done.

THE LESION

The lesion is a developmental defect of vascular embryology, with persistence of bizarre arterial or venous or arteriovenous plexuses at any level and for any distance along the cord. Commonly the lower half is the more frequently affected. Not only may the tangled ramifications be found on the surface, but worse, they may actually pervade cord substance. Careful morphological classification of the individual lesions into venous, arterial and arterio-venous categories has been made (Wyburn Mason, 1943; Turner and Kernohan, 1941; Epstein *et alii*, 1949); but this nice differentiation seems irrelevant to the pattern of clinical presentation.

In essence, any portion or the whole cross-section of the cord at any level may lose its function, either in long-drawn progression or with apoplectic suddenness. The mechanism of cord damage is threefold. First, the diversion of blood into these myriad channels can, *per se*, cause significant cord ischæmia; secondly, there is the possibility of spreading thrombosis, perhaps precipitated by trauma or degenerative change; thirdly, there is the threat of hæmorrhage, either subarachnoid or intramedullary, or both. Space occupation is not a common feature of these lesions, but compression may occur after hæmorrhage or in the very rare cases in which there is an aneurysmal dilatation of one of the vessels (Robertson, 1938; Scoville, 1948; Wyburn Mason, 1943). In this connexion it is relevant to consider the widened, thickened and tortuous spinal arteries, sometimes with aneurysmal formation and cord compression, which can occur in coarctation of the aorta (Wyburn Mason, 1943). But here the malformation is regarded as part of the collateral circulation which develops as a consequence of the coarctation, and not (like cerebral aneurysm) as a coincidental congenital defect. The possibility of disturbance of cord function receives scant mention in accounts of this disease. That it has a practical bearing on contemplated surgical measures is illustrated by Gross and Ladd (1953), who write as follows:

> In two patients aged thirty-one and fifty years respectively there developed during operation a spinal cord damage (presumably ischæmic) which left these subjects with severe nerve weaknesses of both legs. This distressing complication places these two adults in a far worse condition after operation, in spite of cure of hypertension, than they were in before. There was nothing at operation in the way of shock, obliteration of intercostal arteries, etc., that we would blame specifically as being the cause of these disasters.

[1] Received on January 19, 1956.

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However, it should be said that ischæmic necrosis of the spinal cord has been reported to follow chest surgery where no vascular malformation exists. Such a case is reported by Billings and Robertson (1955), who review the anatomy of the blood supply of the spinal cord and show that myelomalacia may follow obstruction of a large radicular artery, and attribute the disaster in their case to damage of an intercostal artery proximal to the spinal branch. " Efocaine " was not used in this case.

DIAGNOSIS

The age of onset of symptoms, as with other neurological vascular anomalies, is commonly in the third, fourth and fifth decades, and though no age is exempt, manifestations are rare in childhood (Buchanan and Walker, 1941 ; Ford, 1950).

The clinical history and physical findings, reflecting the pleomorphic nature of cord involvement, may give no lead in diagnosis. However, spontaneous subarachnoid hæmorrhage, together with cord damage (as occurred in Case III), is almost pathognomonic. If there is no associated cord damage, subarachnoid hæmorrhage due to spinal vascular anomaly may be indistinguishable clinically from that due to rupture of a cerebral saccular aneurysm or angiomatous malformation (Case I). In spinal lesions, no bruit has ever been described. Cardiac failure is not recorded. There are occasional reports of an associated skin nævus, confined in some cases to the corresponding metamere. Final diagnostic confirmation can come only from lumbar puncture, myelography, possibly even laminectomy and, in the last resort, autopsy study.

Lumbar puncture reveals no characteristic features unless subarachnoid hæmorrhage has occurred. Though there may be slight pleocytosis with varying increase in protein, there is often no abnormality in the cerebrospinal fluid. Manometry, in the majority of cases, reveals no block.

Myelography may supply the key to diagnosis. Ethyl iodophenylundecylate (" Pantopaque ") used as a contrast medium will usually display the typical radiographic signs. The contrast medium is at first slightly held up at the lower level of the lesion, and as it spreads between the tortuous vessels it outlines those running parallel to the cord and those at right angles to it. This deposition of the contrast medium between the vessels gives two unmistakable patterns. Those vessels running parallel to the cord show as negative strands of irregular contour. These are illustrated in the figure by the lowermost arrow. Those vessels which run in the plane at right angles to this are shown as ring translucencies. The upper arrows in the illustration designate one of these.

Recently one of us (A.A.M.) had the opportunity of seeing a number of these lesions demonstrated at the National Hospital for Nervous Diseases at Queen Square by Dr. James Bull and Dr. Hugh Davies. The usual

FIGURE I

prone method of myelography did not always adequately delineate the extent of the lesion. In some of these cases the supine position was used, and what appeared in the prone position to be small lesions were demonstrated in the supine position as very extensive lesions. It is well, then, for the radiologist to examine these patients in both the prone and the supine positions.

OUTCOME

It is difficult to imagine any form of treatment that can be of benefit. The problem is very different from that which confronts the surgeon

in cerebral malformations, in which complete delineation of the lesion is possible by angiography, and its situation may give good reason to hope that removal will not endanger vital structures or cause prohibitive disability. In spinal cord lesions, on the other hand, myelography gives little anatomical information, and in any event autopsy studies make it difficult to envisage any place for surgery, though there may be a rare exception. Such a case described by Scoville in 1948 was the removal, in operative circumstances in which there was no choice, of an aneurysm the size of a cherry and a false aneurysmal cyst arising from a vascular malformation in a boy, aged fourteen years. There was good recovery; but the actual compressive nature of the lesion in this case is not a typical experience. Electro-coagulation as practised by Trupp and Sachs (1948) has no other advocates, and deep X-ray therapy has little to commend it, though it appears to have been very widely used.

Reports of Cases

Case I.—D.A., a typist, aged forty-four years, presented with a history which had begun thirty-one years before, when she was thirteen years old. She collapsed at school with severe pain in the neck and the upper part of the chest, vomited and became stuporose. She was kept in bed for some weeks and made a complete recovery. Two exactly similar attacks occurred at the ages of eighteen and twenty-five years. Twelve weeks after the third attack she had a fourth; but on this occasion recovery was not complete, for she now noticed weakness of the left foot. Two years later she began to suffer from weakness and wasting of the left hand. In the ensuing seventeen years before her admission to hospital there had been an insidious increase in motor incapacity in the left upper and lower limbs, so that for two years she had been unable to work. There was no sphincteric disturbance, but on questioning she admitted to an increasing numbness in the right lower limb over the past six years.

Examination of the patient revealed gross pyramidal involvement in the left lower limb with spasticity, weakness, increased tendon reflexes, patellar and ankle clonus and an extensor plantar response. Abdominal reflexes were absent. Pyramidal involvement in the right lower limb was mild, with slight hypertonus, increase in tendon reflexes, an extensor plantar response and minimal weakness. The abdominal musculature was normal. All motor involvement in the left upper limb was of the lower motor neuron type, with weakness and wasting of the deltoid, *pectoralis major*, biceps and all muscles of the forearm and intrinsic muscles of the hand. The triceps reflex was just present, but the biceps and supinator reflexes were absent. Examination of the right upper limb revealed no motor abnormality. Anæsthesia and thermo-analgesia were present in the right lower limb and the right side of the abdomen to the level of the umbilicus, and there was complete sensory loss in the lateral aspect of the left arm, forearm and hand. Lumbar puncture revealed cerebro-spinal fluid normal in cellular and protein content at a pressure of 70 millimetres of water. Manometric findings were normal. Myelographic examination revealed a "hold up" of the contrast medium at the level of the sixth cervical vertebra. Beyond this it delineated a typical angiomatous malformation extending over the length of at least five cervical vertebræ.

At laminectomy (from the third to the sixth cervical vertebræ) a tightly packed plexiform arrangement of veins was seen to be covering the cord in the full length of exposure. These vessels varied in size from one-quarter to one-half centimetre in diameter. The lesion was clearly not surgically remediable. After operation there was an exaggeration of abnormal neurological signs, which was fortunately of short duration, and she was slightly less incapacitated on her discharge from hospital two months later than she had been on admission; but this was probably the result of energetic physiotherapy, which she had not before enjoyed.

Case II.—C.C., a shop assistant, aged forty-seven years, presented with a history which had been complicated by the presence of a disc lesion. For fourteen years he had had attacks, lasting several days and occurring about twice a year, of incapacitating low lumbar backache. Two years before his admission to hospital he had also had pain of right sciatic radiation, which had been almost constant, and which was unrelieved by rest and traction. Eighteen months before his admission to hospital he became increasingly stiff in the right leg, was constipated, and had difficulty in initiating micturition. Ten months before his admission to hospital a herniated intervertebral disc between the fifth lumbar and first sacral vertebræ had been removed elsewhere, with complete relief of his backache and sciatica. However, the stiffness in the right lower limb gradually increased, and he continued to have constipation and difficulty in starting micturition. Three months before his admission to hospital his left leg had become stiff and weak.

Examination of the patient now revealed spastic weakness of both lower limbs against moderate resistance. The knee and ankle reflexes were exaggerated, the abdominal reflexes were absent, and the plantar reflexes were equivocal. Sensation was normal. Lumbar puncture produced cerebro-spinal fluid at a pressure of 110 millimetres of water. Manometry showed no evidence of a block. Five lymphocytes were present per cubic millimetre of fluid, and the protein content was 99 milligrammes per 100 millilitres. The Lange test showed no abnormal precipitation, and the glucose and chloride contents were normal. The Wassermann reaction was negative in the blood and cerebro-spinal fluid. Myelographic examination showed that the column of contrast medium repeatedly broke up in the thoracic region; but there was no evidence of block. This was a technically poor myelogram. A provisional diagnosis of disseminated sclerosis was made.

Eight months later the patient came up for review, and examination now revealed impairment to all forms of sensation below the seventh thoracic vertebra. His motor disability had increased, and he could not take more than a few steps without support. The serious possibility was that a space-occupying lesion had until now been missed. Myelographic examination now revealed typical striated filling defects in the contrast medium in the lower part of the column at the level of the seventh thoracic vertebra. The lesion extended over at least seven spinal segments, and at the upper end a ring shadow was seen (see Figure I).

At laminectomy (fourth to eighth dorsal vertebræ) a large collection of vessels, each two millimetres in diameter, containing dark but not venous blood, was

seen to be overlying the cord opposite the sixth and seventh dorsal vertebræ, forming a tortuous, confused mass on its posterior and medial aspects. The mass appeared to be fed by a long spinal vessel above it; but on temporary constriction of this vessel the flow of blood in the malformation was in no way altered. The constriction was released and the wound was closed without further interference. The patient was discharged from hospital with his condition in no way significantly altered.

CASE III.—G.G., an Italian labourer, aged thirty-two years, who could speak little English, was admitted to hospital as an "emergency", with the history that he had suddenly collapsed to the ground while walking along a street. He had felt a severe pain in the left side of the chest anteriorly, which was followed immediately by pain in the thoracic part of the spine, the shoulder blades and the arms. Within minutes he had lost the power of both lower limbs. There was no loss of consciousness. Until this catastrophe, he had been in excellent health.

Examination of the patient revealed him to be a well-built man in considerable distress, complaining of neck stiffness, occipital headache and pain in the chest, with signs of gross spinal cord lesion with an upper level at the fifth cervical vertebra. Apart from a little movement of his left ankle, there was complete flaccid paraplegia with loss of all lower limb reflexes. The lower intercostal muscles were weak, as were the abdominal muscles. The abdominal and cremasteric reflexes could not be elicited. The right upper limb was normal, but there was flaccid weakness against minimal resistance of all muscle groups in the left upper limb. The left biceps and supinator reflexes were present, but the left triceps reflexes could not be elicted. Hypo-algesia and thermo-anæsthesia between the fifth cervical and the fifth thoracic vertebræ on the left side were the only sensory abnormalities detected. Horner's syndrome was present on the left side. Control of both bladder and rectum was lost. Lumbar puncture produced uniformly blood-stained fluid at a pressure of 140 millimetres of water. Xanthochromia was present. Queckenstedt's test showed no evidence of block. The Wassermann reaction was negative in the blood and cerebro-spinal fluid.

A diagnosis of spinal vascular anomaly was made, and conservative management was advised. Over the course of the next three weeks there appeared to be slight but definite improvement in motor power; but within a few days, without any eloquent episode, the patient was reduced to the neurological state which he had presented on his admission to hospital. Myelography by the cisternal route showed an irregular column of contrast medium occupying the cervical region to the seventh cervical vertebra. Further flow in a caudal direction showed a slight hold-up in the region between the first and second thoracic vertebræ. The disposition of the contrast medium was extremely suggestive of a vascular anomaly.

Laminectomy from the sixth cervical to the second dorsal vertebra showed an angiomatous malformation surrounding the cord with many large veins two to three centimetres in diameter, some perforating the dura to connect with epidural veins. Clearly nothing could be done, and the patient has shown no significant change since operation.

DISCUSSION

Wyburn Mason's opinion that many cases of so-called "myelitis" are in reality examples of vascular malformations received striking confirmation from the Montefiore Hospital for Chronic Diseases, New York. Here Brion and his colleagues in 1952 reviewed 31 cases with autopsy in which there had been a clinical picture of "transverse or diffuse myelitis". In no less than nine cases the lesion was myelomalacia secondary to vascular anomaly. Correct diagnosis before death had been made in only two cases, and in both operation had provided the answer. Of the seven undiagnosed cases three, after the performance of laminectomy, had been labelled "intramedullary tumour with recent hæmorrhage", a fourth was thought to be neurosyphilis, and the remaining three received such non-committal appellations as "degenerative disease of the spinal cord" and "myeloradiculopathy". It is likely that this experience at the Montefiore Hospital is reflected unrecognized in innumerable institutions for the chronically ill where autopsy study is not secured. Spinal vascular anomalies thus continue to be considered a rarity.

Our own small experience in three cases illustrates the varied presentation and symptomatology that can occur. In Case I it now seems reasonable to assume that the attacks of pain in the neck, vomiting and stupor were due to subarachnoid hæmorrhage from the spinal vascular anomaly. No lumbar puncture was performed at the time; but if the diagnosis of subarachnoid hæmorrhage had been confirmed, there would have been nothing in the first three attacks to focus attention on the cord. A diagnosis of ruptured cerebral aneurysm could well have been made. In Case II the possibilities firstly of disseminated sclerosis and then of spinal tumour were both considered before the nature of the lesion was apparent. Only in Case III was there little doubt about diagnosis once lumbar puncture had been performed.

All three patients were subject to laminectomy, two without benefit (Cases II and III) and one with subsequent slight improvement, probably unconnected with operation (Case I). In Case III there was some initial improvement after the patient's admission to hospital. Had deep therapy been used or operation resorted to at this stage, it would have been less obvious that improvement was spontaneous. It may seem that the three laminectomies were unjustified and should not have been undertaken. Certainly the grave implications of telling the patient that he has a vascular anomaly for which there is no treatment must be accepted, provided one can be certain of the diagnosis. It may be that laminectomy is the only means of ensuring such certainty.

SUMMARY

Three cases of spinal vascular anomaly are described. They illustrate the varied methods of presentation, the difficulties of diagnosis and the ineffectiveness of treatment apart from purely palliative measures. It is suggested that this lesion may so often mimic other affections of the spinal cord that its presence may not be considered or recognized.

ACKNOWLEDGEMENT

We should like to thank Dr. J. P. Ainslie for permission to report the case histories of these patients referred to his care, and for the stimulus to us given by his interest.

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A B O BLOOD GROUPS AND GASTRO-DUODENAL DISEASES[1]

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AIRD *et alii* (1953) demonstrated an association between carcinoma of the stomach and blood group A in the United Kingdom. Further observations both in England and in Denmark have widened the scope of investigations into the associations of A B O blood groups and gastro-duodenal diseases.

In England after Aird *et alii* (1954) had shown a relationship between chronic peptic ulcer and blood group O, Clarke *et alii* (1955) demonstrated that this association was true for chronic duodenal ulcer only, and that the distribution of A B O blood groups in patients with chronic gastric ulcer did not differ significantly from that in a control non-ulcer population. Similar observations were made by Køster *et alii* (1955) in Denmark, and they postulated that these associations could be related to changes in the acid-secreting capacity of the stomach.

The investigation reported here was undertaken to ascertain whether these associations of gastro-duodenal diseases and A B O blood groups were valid for Australia. Certain new facts have emerged which have a bearing not only on the associations between genetically-determined blood groups and gastro-duodenal diseases but also upon the location of lesions in the stomach.

MATERIAL

Records of public in-patients at Royal Prince Alfred Hospital, Sydney, have been analysed during the period 1947–1954.

As not all in-patients have routine blood grouping, only those cases in which data were available by virtue of transfusion for bleeding or surgical intervention could be admitted to this series. No cases were included from immigrants. Certain selective criteria were employed.

Chronic Gastric Ulcer. Only those cases of chronic gastric ulcer with microscopic evidence of chronicity and non-malignancy at autopsy or in resection specimens were admitted. In addition only those cases in which the site of the lesion was indisputable were allowed. They were divided into two classes: (*a*) those designated prepyloric, in which the chronic gastric ulcer was situated in the prepyloric region, that is, within the pyloric antrum or within 4·0 centimetres of the pylorus in the gross specimen; (*b*) those designated non-prepyloric in which the chronic gastric ulcer was situated elsewhere in the stomach. If an ulcer was found at each site in one subject, the subject's blood group was admitted to both classes (seven instances).

Carcinoma of the Stomach. Cases of carcinoma of the stomach were admitted in which there was microscopic proof of the nature of the lesion (at autopsy or after resection) or in which exploratory laparotomy showed macroscopic evidence of gastric carcinoma with metastatic deposits in the liver or on the peritoneum. Cases were allowed only in which the site of origin of the lesion was obvious; they were classified as for chronic gastric ulcer. Cases in which carcinomatous involvement of the stomach was diffuse were not allowed.

Chronic Duodenal Ulcer. Cases of chronic duodenal ulcer were admitted in which there was microscopic evidence of site and chronicity at autopsy or on resection, or in which there was a combination of radiological and macroscopic evidence at laparotomy for resection, when the resected specimen did not contain the ulcer.

No cases were allowed in which there was any combination of gastric and duodenal ulcer, or gastric carcinoma with chronic peptic ulcer.

Controls

The figures of Walsh (1947) for the A B O blood group distribution of 30,000 consecutive donors to the New South Wales Red Cross Blood Transfusion Service were taken. In addition, as a hospital control, the A B O blood groups of all general hospital recipients in 1950 were obtained, with the omission of those who received transfusions for gastro-duodenal diseases or their surgery, or gastro-intestinal bleeding.

[1] Received for publication on March 21, 1956.

[2] Working on a part-time Research Grant from the Royal Australasian College of Physicians.

TABLE I

The A B O Blood Group Distribution in N.S.W. Blood Donors, Hospital Recipients and Patients with Chronic Duodenal Ulcer, Chronic Gastric Ulcer and Gastric Carcinoma (Percentages of Total in Parentheses).

Population	Total Number	A	B	O	AB
N.S.W. blood donors	30,000	11,514 (38·38%)	2,912 (9·70%)	14,672 (48·91%)	902 (3·01%)
Hospital recipients	628	235 (37·4%)	52 (8·3%)	327 (52·1%)	14 (2·2%)
Chronic duodenal ulcer	192	46 (24·0%)	12 (6·2%)	130 (67·7%)	4 (2·1%)
Gastric ulcer:					
Prepyloric	83 (35·0%)	52 (62·7%)	7 (8·4%)	22 (26·5%)	2 (2·4%)
Non-prepyloric	154 (65·0%)	47 (30·5%)	11 (7·1%)	94 (61·1%)	2 (1·3%)
Total	237	99 (41·8%)	18 (7·6%)	116 (48·9%)	4 (1·7%)
Gastric carcinoma:					
Prepyloric	97 (38·5%)	57 (58·8%)	10 (10·3%)	24 (24·7%)	6 (6·2%)
Non-prepyloric	155 (61·5%)	40 (25·8%)	12 (7·7%)	92 (59·4%)	11 (7·1%)
Total	252	97 (38·5%)	22 (8·7%)	116 (46·0%)	17 (6·8%)

RESULTS

The results of the compilation are shown in Table I and the analysis is summarized in Table II.

Controls

In taking controls for this type of study, it is important that a large number should be employed. The results of A B O blood grouping from blood donors from the same area are convenient and likely to be unbiassed (Aird *et alii*, 1954). It is, however, necessary to show that the A B O blood group distribution in the hospital under consideration does not differ significantly from that of the blood donors from the same area. This can be done in two ways. Firstly, it can be shown in a disease in which there is no definite association with the A B O blood groups that there is no significant difference in blood group distribution between the hospital population suffering from this disease and the blood donor population. It has previously been reported (Billington, 1956*a*) that, in the period under consideration, the A B O blood group distribution in Royal Prince Alfred Hospital bronchiectasis patients did not differ significantly from that of New South Wales Red Cross blood donors. Secondly, in this instance in which transfusions were given in all cases it can be shown that the A B O blood group distribution in the general hospital population of patients receiving blood transfusions, when gastro-duodenal diseases are excluded, does not differ significantly from that in the blood donor series ($\chi^2=3\cdot81$ with two degrees of freedom, taking groups B and AB together; $P>0\cdot1$) (see Table II).

TABLE II

Analysis of Comparisons between O : A : B+ Ratios

Comparison	χ^2 for Heterogeneity (D. of F. = 2)	Probability
Blood donors *v.* hospital recipients	3·81	>0·1
Blood donors *v.* duodenal ulcer	27·18	<0·001
Blood donors *v.* total gastric ulcer	2·48	>0·2
Blood donors *v.* total gastric carcinoma	1·96	>0·3
Blood donors *v.* prepyloric ulcer	21·40	<0·001
Blood donors *v.* non-prepyloric ulcer	9·34	<0·01
Blood donors *v.* prepyloric carcinoma	23·07	<0·001
Blood donors *v.* non-prepyloric carcinoma	10·41	<0·01
Prepyloric ulcer *v.* non-prepyloric ulcer[1]	26·73	<0·001
Prepyloric carcinoma *v.* non-prepyloric carcinoma[1]	32·28	<0·001
Prepyloric ulcer *v.* prepyloric carcinoma[1]	1·17	>0·3
Non-prepyloric ulcer *v.* non-prepyloric carcinoma[1]	3·30	>0·1
Blood donors *v.* total prepyloric lesions	43·41	<0·001
Blood donors *v.* total non-prepyloric lesions	16·76	<0·001
Duodenal ulcer *v.* total non-prepyloric lesions[1]	4·90	>0·05
Prepyloric lesions *v.* total non-prepyloric lesions[1]	58·72	<0·001

[1] Calculated on the basis of contingency tables.

It therefore appears legitimate to compare the A B O blood group distribution of the hospital populations under consideration with that of the blood donor population.

It will be admitted that the cases of gastro-duodenal diseases analysed in this series are highly selected, and any general conclusions reached cannot be accepted as statistically proven until evidence is forthcoming to show that such selection does not affect the results.

Chronic Duodenal Ulcer

This small series shows that there is a highly significant association between chronic duodenal ulcer and blood group O ($\chi^2=27\cdot18$ with 2 degrees of freedom; $P<0\cdot001$). This agrees with previously reported findings from England and Denmark. The incidence of blood group O is 18·8% higher in these chronic duodenal ulcer subjects than in the control population.

Chronic Gastric Ulcer

As in England, the total figures for chronic gastric ulcer show no significant difference in the A B O blood group distribution when compared with the blood donor series ($\chi^2=2\cdot48$ with 2 degrees of freedom; $P>0\cdot2$).

However, if chronic gastric ulcer cases are divided according to site into two groups, prepyloric and non-prepyloric, there is a significant difference as far as A B O blood group distribution is concerned between the two groups ($\chi^2=26\cdot73$ with 2 degrees of freedom; $P<0\cdot001$).

Moreover, in both the prepyloric ulcer and non-prepyloric ulcer groups the A B O blood group distribution differs significantly from the control population. For prepyloric ulcer there is an increased incidence of group A, 24·3% above the control ($\chi^2=21\cdot40$ with 2 degrees of freedom; $P<0\cdot001$); for non-prepyloric ulcer there is an increased incidence of group O, 12·1% above the control ($\chi^2=9\cdot34$ with 2 degrees of freedom; $P<0\cdot01$).

Gastric Carcinoma

Contrary to the findings of Aird *et alii* (1953) for the United Kingdom, no overall predominance of group A is found in this series of gastric carcinoma; there is no significant difference in A B O blood group distribution when compared with controls ($\chi^2=1\cdot96$ with 2 degrees of freedom; $P>0\cdot3$). However, as with chronic gastric ulcer, two significantly different populations as regards A B O blood group distributions are found according to whether the carcinoma arose in the prepyloric or non-prepyloric region ($\chi^2=32\cdot29$ with 2 degrees of freedom; $P<0\cdot001$). Prepyloric carcinoma shows a significantly higher incidence of group A, 19·6% above the controls ($\chi^2=23\cdot07$ with 2 degrees of freedom; $P<0\cdot001$) and non-prepyloric carcinoma a higher incidence group O, 10·4% above the controls ($\chi^2=10\cdot41$ with 2 degrees of freedom; $P<0\cdot01$).

Aird *et alii* (1954) showed in a series of 2,745 cases of carcinoma of the stomach an $\frac{A}{A+O}$ ratio of $\frac{46\cdot19}{89\cdot14}$ with a predominance of group A subjects when compared with a control population. If one applies the $\frac{A}{A+O}$ ratio found in the present series, taking prepyloric and non-prepyloric carcinoma separately, the figures of Aird *et alii* could be explained on the present data if 74·3% of the United Kingdom carcinomata were situated in the prepyloric region.

This figure does not differ greatly from the commonly accepted incidence of prepyloric carcinoma as a proportion of the total. Hurst and Stewart (1929) in England found 66·5% of a total of 164 autopsy examples of gastric carcinoma occurring in the pyloric antrum, and Stout (1953) found 73·3% of a total of 120 resection specimens of gastric carcinoma arising within 4·0 centimetres of the pylorus. The incidence of prepyloric carcinoma in the present series is only 38·5% of the total. This discrepancy is unexplained, but it seems unlikely to be due entirely to differences in selection as 86·6% of the prepyloric carcinomata and 74·8% of the non-prepyloric carcinomata were examined pathologically, either at autopsy or after resection. Further, during the same period at another metropolitan teaching hospital (Sydney Hospital), 118 cases of gastric carcinoma were reviewed in which the site of origin was determined either at autopsy or after resection, 45 (38·1%) of these were classifiable as prepyloric (Billington, 1956*b*).

Site of Gastric Lesions in Relation to A B O Blood Groups

It appears obvious to compare prepyloric lesions, and non-prepyloric lesions, irrespective of their nature as far as A B O blood group distribution is concerned (Table III).

TABLE III

Comparison of A B O Blood Group Distribution in Gastric Lesions (Carcinoma and Chronic Peptic Ulcer) According to Site

Site	Total	A	B	O	AB
Prepyloric ..	180	109 (60·6%)	17 (9·4%)	46 (25·6%)	8 (4·4%)
Non-prepyloric	309	87 (28·2%)	23 (7·4%)	186 (60·2%)	13 (4·2%)

χ^2 for heterogeneity (D. of F.=2)=58·72.

There is no significant difference in the A B O blood group distribution in prepyloric lesions when carcinoma is compared with chronic peptic ulcer ($\chi^2=1\cdot17$, with 2 degrees of freedom; $P>0\cdot3$); nor is there a significant difference in a similar comparison of non-prepyloric lesions ($\chi^2=3\cdot30$ with 2 degrees of freedom; $P>0\cdot1$).

Furthermore, prepyloric lesions and non-prepyloric lesions constitute two significantly different populations as far as A B O blood group distribution is concerned ($\chi^2=58\cdot72$ with 2 degrees of freedom; $P<0\cdot001$), and both differ significantly from the control population. Prepyloric lesions show a

significantly higher incidence of group A, 22·2% above the control population (χ^2=43·41 with 2 degrees of freedom; P<0·001), and non-prepyloric lesions a higher incidence of group O, 11·3% above the control population (χ^2=16·76 with 2 degrees of freedom; P<0·001).

It would appear from these figures that as far as the stomach is concerned association with A B O blood groups bears some specific relationship to the location of the lesions, irrespective of its nature.

Sex

The chronic duodenal ulcer series comprised 162 male and 30 female subjects; the chronic gastric ulcer series comprised 143 males (52 prepyloric and 91 non-prepyloric) and 94 females (31 prepyloric and 63 non-prepyloric); the gastric carcinoma series comprised 184 males (65 prepyloric and 119 non-prepyloric) and 68 females (32 prepyloric and 36 non-prepyloric).

TABLE IV
Gene Frequencies

Group	Total	A	B	O	χ^2 for Unreasonableness of Group Proportions (D. of F. = 1)
Blood donors	30,000	0·235	0·066	0·698	—
Duodenal ulcer	192	0·136	0·038	0·826	1·29
Prepyloric lesions ..	180	0·417	0·085	0·498	1·10
Non-prepyloric lesions ..	309	0·166	0·047	0·787	11·78

There was no significant sex difference in A B O blood group distribution in any of these groups, nor in the gastric lesions could any significant sex difference be detected between prepyloric and non-prepyloric lesions.

An interesting clinical side issue is evident. The exact localization of chronic ulcers in the immediate proximity of the pylorus is often difficult after fluoroscopy (Davis *et alii*, 1955). On the basis of the figures given above, taking sex and the distribution of surgical ulcer lesions into consideration, the knowledge of the A B O blood group of any one subject may help in assessing the actual site of the ulcer. In males, if the blood group is O, the odds are 7 to 1 in favour of the ulcer being on the duodenal side of the pylorus, but if the blood group is A, there is an even chance that the ulcer may be on the gastric side. In females, if the blood group is O, the odds are 3 to 1 in favour of the ulcer's being in the duodenum, but if the blood group is A, the odds are 5 to 2 in favour of its being prepyloric.

Gene Frequencies

Table IV gives the A B O gene frequencies calculated by the method of Dobson and Ikin (1946) for chronic duodenal ulcer, prepyloric lesions and non-prepyloric lesions. It will be seen that the χ^2 for unreasonableness of group proportions is not significant in the cases of chronic duodenal ulcer and prepyloric gastric lesions. However, in the case of non-prepyloric gastric lesions the χ^2 has a value of 11·79 with 1 degree of freedom. The reason for this finding is not at once apparent, but as the gastric lesions have been divided according to site, it is certainly a possibility that non-prepyloric lesions do not constitute a homogeneous population as far as A B O blood group distribution is concerned, and further studies may be directed to showing whether there are any other A B O blood group localization associations within the stomach, for example, cardiac lesions and blood group A.

Chronic Duodenal Ulcer and Non-Prepyloric Lesions

Both non-prepyloric lesions and chronic duodenal ulcer have shown significant differences in the A B O blood group distribution when compared with the controls; the differences in each instance show a higher incidence of group O, and it is conceivable that these two populations are similar as far as A B O blood group distribution is concerned. A statistical comparison between the two populations gives a χ^2 value of 4·90 with 1 degree of freedom (P>0·05). It is possible that a greater correlation may be found if non-prepyloric gastric lesions are capable of subdivision on the basis of further site—A B O blood group associations.

DISCUSSION

The association between certain disease states and differences from control values in the distribution of genetically determined blood groups suggests that there may be some genetic relationship between blood groups and these diseases. In the case of gastro-duodenal lesions, it is known that there is a definite hereditary factor in both carcinoma of the stomach (Videbaek and Mosbech, 1954; Macklin, 1955) and chronic peptic ulcer (Doll and Buch, 1950) and that there is some site specificity in the hereditary factor in chronic peptic ulcer (Doll and Kellock, 1951).

It has been postulated by Køster *et alii* (1955) that differences in the A B O gene frequencies in gastro-duodenal diseases may be related to differences in gastric acid production; for it has been demonstrated that there is an increased parietal cell mass in duodenal ulcer (Hunt and Kay, 1954) with group O predominance, carcinoma of the stomach (alleged group A predominance) is often associated with achlorhydria and pernicious anæmia has been associated with blood group A (Buchanan and Higley, 1921).

The finding in this investigation that the associations between gastric diseases and A B O blood groups are related to the sites of the lesions rather than their nature tends to disprove the acid production hypothesis. Although few parietal cells exist in the prepyloric region (Berger, 1934) there is no evidence that the acid secretory pattern of the stomach shows significant variation according to the location of lesions within the stomach in the absence of pyloric obstruction. Indeed, an analysis of the unique data of Ihre shows that in the case of chronic peptic ulcer there is no significant difference in the resting output of acid (in uncontaminated gastric juice) between prepyloric and non-prepyloric lesions ($P>0\cdot6$).

It seems more profitable to examine an hypothesis, first suggested by Aird *et alii* (1954), that the A B O genes in some way are associated with susceptibility or resistance of the gastric and duodenal mucosæ to chronic peptic ulceration and carcinoma. In view of the findings of this investigation it would seem that in the case of the stomach, such resistance or susceptibility factors appear to affect, in different ways, separate sites of the stomach to both ulcerogenic and carcinogenic influences.

If this hypothesis is examined with reference to the figures in Table III, three possibilities exist: either a linkage with blood gene A is associated with susceptibility of the prepyloric mucosa and protection of the non-prepyloric mucosa, or a linkage with blood group gene O is associated with protection of the prepyloric mucosa and susceptibility of non-prepyloric mucosa or linkages with both genes may operate. On examining the gene frequencies, it can be calculated that although blood group gene B is infrequent throughout, there is no demonstrable difference in its frequency compared with controls either in chronic gastric ulcer, gastric carcinoma or according to whether these lesions are prepyloric or non-prepyloric (Table V). This is in accordance with the findings in England for the frequency of gene B in controls compared with chronic gastric ulcer (Clarke *et alii*, 1955) and gastric carcinoma (Aird *et alii*, 1954). This could be taken to imply that at least in association with gene B, there are no mucosal protection or susceptibility factors which might be related to genes A and O; and further the distribution of gastric lesions in association with gene B, according to site, is independent of any site-protection or site

Table V

Comparison of Frequencies of Incidence of Gene B

Comparison	χ^2 for Heterogeneity (D. of F.=1)	Probability
Blood donors *v.* prepyloric lesions	1·05	>0·3
Blood donors *v.* non-prepyloric lesions	1·83	>0·1
Blood donors *v.* duodenal ulcer..	1·46	>0·2
Prepyloric lesions *v.* non-prepyloric lesions[1]	2·84	>0·05

[1] Calculated on the basis of contingency tables.

susceptibility factors which might be related to genes A and O. Table VI shows the incidence of prepyloric and non-prepyloric lesion in association with A, B and O genes. A comparison of the $\frac{\text{prepyloric}}{\text{non-prepyloric}}$ ratio of lesions according to gene can be made and the effects of genes A and O upon the ratio in association

Table VI

Contingency Table Showing the Ratio of Distribution of Gastric Lesions According to A B O Gene Presence

Gene	Prepyloric Lesions	Non-Prepyloric Lesions	χ^2 for Difference from Gene B (D. of F.=1)
B	15·3	14·5	—
A	75·0	51·3	0·61 (P>0·30)
O	89·7	243·2	7·99 (P<0·01)

with gene B can be assessed. In the case of gene A, there is no significant difference in $\frac{\text{prepyloric}}{\text{non-prepyloric}}$ ratio when compared to the ratio in association with gene B ($\chi^2=0\cdot61$ with 1 degree of freedom; $P>0\cdot30$), but with gene O there is a significant difference in the $\frac{\text{prepyloric}}{\text{non-prepyloric}}$ ratio in comparison with gene B ($\chi^2=7\cdot99$ with 1 degree of freedom; $P<0\cdot01$).

In this small series of cases, therefore, the evidence suggests that if a relationship to a

single gene is involved then blood group gene A does not appear to be related to any prepyloric susceptibility or non-prepyloric protection and that the gene O may in some way be associated with prepyloric protection and non-prepyloric mucosal susceptibility to both ulcerogenic and carcinogenic influences in the stomach. However, there is no direct evidence to suggest that the hypothesis, within which these conclusions are reached, is the correct one, as the essential relationship between A B O blood groups and gastro-duodenal lesions is at present unknown.

In connexion with the associations of A B O blood groups and gastro-duodenal diseases, it is well recognized that certain individuals possess the ability to secrete the specific blood group mucopolysaccharides A, B and H substances in saliva, gastric juice and elsewhere, corresponding to the blood group of the individual; H substance is present in subjects of group O and may be present to a less extent in individuals of other blood groups. These positive secretors constitute 73·4% of the population in Australia (Simmons *et alii*, 1951). In the gastric juice it appears that these substances are produced by the mucus-secreting cells (Osborn, 1952). There is relatively little information on the salivary secretor status of patients with gastro-duodenal diseases, except that there appears to be a correlation between duodenal ulcer and salivary non-secretors when compared with a control population (Clarke, 1955). No information is available on the gastric secretor status in subjects with gastro-duodenal diseases nor on the sites within the stomach of the mucous cells which secrete the blood group substances.

There is information, however, that certain other qualitative differences exist in the types of mucus produced by the prepyloric and non-prepyloric gastric mucosa in man (Glass, 1953). A specific glandular mucoprotein is secreted by the body and fundus of the stomach, but not from the prepyloric or cardiac regions. This substance is not present in saliva. It is not present in the fasting gastric secretion of all normal individuals, or those with gastric ulcer; it appears to be present in increased amounts in the fasting gastric juice of subjects with duodenal ulcer, but no information is available upon any relationship between the secretion of this substance and the A B O blood groups of the subjects investigated. It is absent in all cases of pernicious anæmia and may contain Castle's intrinsic factor, as it is capable of enhancing the absorption of orally administered vitamin B_{12} in subjects with pernicious anæmia (Glass, 1953). Another preparation of gastric mucus which also has considerable intrinsic factor activity, is known to contain blood group substance (Springer *et alii*, 1954).

An interesting observation which pertains to differences in gastric mucus in gastric disease, according to the site of the lesion, is reported by Wolf *et alii* (1953). In 21 patients with carcinoma of the stomach, there was an absence in the gastric secretion of the specific glandular mucoprotein of Glass, both in the fasting state and after insulin hypoglycæmia; 19 of these patients had carcinoma involving the body of the stomach. In a further 13 patients with gastric carcinoma but without impairment of glandular mucoprotein secretion by the stomach, seven had lesions located in the prepyloric region and three had lesions near the cardia.

It is obvious that, at present, there is no clear-cut explanation of the relationship between A B O blood groups and gastro-duodenal diseases, and the localization of lesions in the stomach. It would appear likely that such a relationship may be less concerned with acid secretion than with qualitative differences in the mucous secretions of the stomach, especially pertaining to differences in susceptibility or resistance of separate sites to carcinogenic and ulcerogenic factors.

Further work is necessary to confirm the findings recorded in this investigation, particularly to prove the associations between A B O blood groups and the site of gastric lesions irrespective of their nature, to ascertain whether further site-blood group associations can be made in the non-prepyloric areas of the stomach, and to demonstrate that the highly selective criteria employed for acceptance in these series do not invalidate the general results.

Finally, before an attempt is made to explain the associations between A B O blood groups and gastro-duodenal diseases, studies may be directed to establishing qualitative differences between the separate gastric and duodenal mucous secretions in normal subjects, and in patients with gastro-duodenal diseases with particular regard to their A B O blood group and secretor status.

Summary

Further evidence is adduced from an Australian population that there is an association between chronic duodenal ulcer and blood group O.

No significant difference in the A B O blood group distribution has been found between controls and cases with chronic gastric ulcer taken as a whole.

Chronic gastric ulcer may be divided into two significantly different populations with regard to A B O blood group distribution according to the site of the ulcer. Differing significantly from a control population, prepyloric ulcer appears to be associated with blood group A, and non-prepyloric ulcer with group O.

Carcinoma of the stomach in this small Australian series has not been found to be associated with blood group A.

Carcinoma of the stomach can also be divided into two significantly different populations with regard to A B O blood group distribution according to the site of origin of the neoplasm. Differing significantly from a control population, prepyloric carcinoma appears to be associated with blood group A and non-prepyloric carcinoma with blood group O.

The association between carcinoma of the stomach and blood group A found in the United Kingdom may be explained by a higher proportion of prepyloric carcinoma than in the present series. The lower proportion of prepyloric carcinoma in this series is unexplained.

Associations between chronic gastric ulcer and gastric carcinoma and the A B O blood groups appear to be governed in part by the site of lesions, prepyloric lesions being associated with blood group A and non-prepyloric lesions with blood group O, irrespective of the nature of the lesions.

No evidence is at present forthcoming to show the essential explanation of the associations between A B O blood groups and gastro-duodenal diseases. It seems possible that gastric mucous secretions may be more important than gastric parietal (acid) secretion in such associations.

If A B O blood groups are associated with gastric resistance or susceptibility factors, then, from this small series, if a relationship to a single gene is involved, it would appear that an association with blood group gene O is more likely to be implicated, with protection of the prepyloric mucosa to both ulcerogenic and carcinogenic factors.

Further work is necessary to confirm these observations elsewhere; studies may also be directed to establishing qualitative differences between the gastric and duodenal mucous secretions in normal subjects and in patients with gastro-duodenal diseases with particular regard to their A B O blood group and secretor status.

Acknowledgements

I wish to acknowledge the permission of the General Superintendent, Royal Prince Alfred Hospital, to obtain access to the records, and to thank Miss R. Bull of the Hospital Staff of Medical Record Librarians for happy co-operation and help in locating the records, and Dr. R. J. Walsh, of the New South Wales Red Cross Blood Transfusion Service, for constantly helpful advice.

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CORRIGENDUM

WE are informed that two errors have occurred in the paper entitled "A Note on the Distribution of A B O Blood Groups in Bronchiectasis and Portal Cirrhosis", by B. P. Billington, which appeared in the issue of February, 1956. In the second column of Table I, on page 20, the total number of blood donors should be 30,000, not 3000. On page 22, in the seventh line of the second column, "group A" should read "gene A". We regret these mistakes.

AUSTRALASIAN MEDICAL PUBLISHING CO. LTD.
SEAMER AND ARUNDEL STS., GLEBE, SYDNEY